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ORIGINAL

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Maureen K. Ohlhausen, Acting Chairman**
Terrell McSweeny

In the Matter of:

IMPAX LABORATORIES, INC.,

a corporation.

Docket No. 9373

RESPONDENT IMPAX LABORATORIES, INC.'S MEMORANDUM OF LAW IN OPPOSITION TO COMPLAINT COUNSEL'S MOTION FOR PARTIAL SUMMARY DECISION

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I. INTRODUCTION

There would be ***no*** Opana ER—branded or generic—available to consumers today absent Impax's settlement with Endo. Yet, in this rule-of-reason case, Complaint Counsel urges the Commission to ignore that competitive reality. It contends that an agreement's competitive effects must be judged based solely on the circumstances existing at the time the agreement was executed, no matter what procompetitive benefits have actually flowed from the agreement. Complaint Counsel argues in particular that *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013), requires the Commission to prospectively and categorically preclude any defense that touches on post-execution evidence. The Motion attacks Impax's Defense No. 8, which simply recites the rule of reason and contends that procompetitive justifications for the Settlement and License Agreement ("SLA") outweigh any purported anticompetitive effects.[1]

Complaint Counsel's sweeping request seeks to wipe away seven years of actual competitive effects. It would exclude from the Commission's rule-of-reason analysis an array of evidence regarding the SLA's procompetitive benefits, including evidence that the agreement allowed Impax: (1) to make its generic Opana ER available to consumers well before the expiration of numerous patents currently blocking all other Opana ER ANDA filers; (2) to remain consistently on the market without fear of injunction or crushing patent-damages liability; and (3) to serve as the ***only*** Opana ER supplier beginning September 1, 2017.

Certainly those are inconvenient facts for Complaint Counsel. But closing the courtroom door to actual competitive-effects evidence is not the solution. Complaint Counsel's approach

[1] Defense No. 8 states in full: "The alleged conduct had substantial pro-competitive justifications, benefited consumers and the public interest, and avoided potential infringement of valid patents. These pro-competitive justifications outweigh any alleged anticompetitive effects of the alleged conduct. There were no less restrictive alternatives that could have achieved these same pro-competitive outcomes." (Leefer Decl. Ex. B , Eighth Defense.)

finds no support in more than 100 years of rule-of-reason jurisprudence. To the contrary, Complaint Counsel's position contradicts foundational antitrust principles and fails as a matter of common sense.

Under the rule of reason, "the factfinder weighs ***all of the circumstances of a case*** in deciding whether a restrictive practice should be prohibited as imposing an unreasonable restraint on competition." *Cont'l T.V., Inc. v. GTE Sylvania, Inc.*, 433 U.S. 36, 49 (1977) (emphasis added). Appropriate factors "to take into account include 'specific information about the relevant business' and 'the restraint's history, nature and ***effect***.'" *Leegin Creative Leather Prods., Inc. v. PSKS, Inc.*, 551 U.S. 877, 885-86 (2007) (emphasis added; citing *State Oil Co. v. Khan*, 522 U.S. 3, 10 (1997)). This entails examining the relevant market both "***before and after*** the restraint was imposed." *Bd. of Trade of Chicago v. United States*, 246 U.S. 231, 238 (1918) (emphasis added). These long-settled principles require the Commission to consider competitive reality, not some narrow slice of time.

Complaint Counsel's Motion is a preemptive strike on its burden to prove a *prima facie* case under the rule of reason. It must be rejected for three fundamental reasons.

First, Complaint Counsel seeks to apply a quick-look approach to reverse-payment settlements. It contends that any patent settlement containing a large reverse payment likely harms competition, and that the burden immediately and automatically falls on defendants to show that the payment was procompetitive. The Supreme Court rejected this approach in *Actavis*, stating unambiguously that "the FTC must prove its case as in other rule-of-reason cases." 133 S. Ct. at 2237. No presumptions exist.

Second, Complaint Counsel's Motion is inconsistent with well-established rule-of-reason analysis. It would severely truncate the far-ranging factual inquiry essential to that analysis,

preventing Impax from offering evidence of actual procompetitive effects. It would also impermissibly relax Complaint Counsel's *prima facie* burden. Specifically, Complaint Counsel asks the Commission to (1) temporally limit the rule-of-reason inquiry to the moment an alleged reverse-payment settlement is executed,[2] and (2) categorically label as anticompetitive every hypothetical restraint on future competition, no matter how unlikely, and even when actual events have disproven the hypothesis. But that approach would break with the entire canon of rule-of-reason jurisprudence which requires Complaint Counsel to demonstrate that the SLA imposes adverse effects on competition, taking into account actual impact, including conditions before and after the agreement was executed.

Third, the specific "defenses" attacked in Complaint Counsel's Motion—(1) entry before patent expiration, (2) the benefits of a reverse-payment settlement generally, and (3) Endo's success in enforcing its patents against all Opana ER ANDA filers except Impax—are strawmen. Impax has not yet fully articulated the SLA's procompetitive justifications or the facts underlying Defense No. 8, and Impax certainly has never said that any of these justifications should be considered in isolation. Nevertheless, the SLA's procompetitive benefits are highly relevant to the traditional rule-of-reason analysis. And Impax should not be barred from offering procompetitive effects evidence in its defense.

The Motion must be denied.

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[2] For its part, Complaint Counsel ignores this limitation. It repeatedly claims that a payment made to Impax years after execution of the settlement agreement is a relevant reverse payment. (Leefer Decl. Ex. A ¶¶ 58-59, 70, 73.) Complaint Counsel cannot have it both ways; it cannot rely on *ex post* evidence when Complaint Counsel finds it useful and then ask the Commission to categorically exclude from consideration competitive realities that Complaint Counsel finds unhelpful.

II. BACKGROUND

A. Factual Background.[3]

In June 2007, Impax was the first to file an Abbreviated New Drug Application ("ANDA") for various dosages of Opana ER, an extended-release opioid used to treat moderate and severe pain. (*See* CC's Statement of Undisputed Facts ¶¶ 9, 12.) The Food and Drug Administration ("FDA") granted Impax tentative approval in May 2010. (*Id.* ¶ 16.)

Endo Pharmaceuticals, the manufacturer of brand-name Opana ER and owner of patents covering that drug, sued Impax for patent infringement in January 2008. (*Id.* ¶ 16; Hassi Decl. Ex. GG,[4] *see* Complaint, ECF No. 1, No. 2:09-cv-0831-KSH-PS (D.N.J. Jan. 25, 2008)). The court in that case eventually ruled in favor of Endo on issues of claim construction, significantly weakening Impax's non-infringement defense. Hassi Decl. Ex. H, Order on Claim Construction, ECF No. 188, No. 2:09-cv-0831-KSH-PS (D.N.J. Mar. 30, 2010). The patent infringement trial began on June 3, 2010. (*See* CC's Statement of Undisputed Facts ¶ 17.)

Impax never gave serious consideration to launching "at-risk"—i.e., prior to a final, non-appealable court decision resolving all liability risk in its patent-infringement litigation with Endo. (Statement of Disputed Facts ¶¶ 1-4.)[5] Before Impax could launch generic Opana ER "at-risk" Impax would need [redacted] (*Id.* ¶ 3.) [redacted]

[redacted]

[3] Although Impax does not dispute most of the facts advanced in Complaint Counsel's Motion, Impax does dispute material facts, including whether it received a large and unjustified payment.

[4] All references to "Hassi Decl." refer to the "Declaration of Edward D. Hassi In Support of Respondent Impax Laboratories, Inc.'s Opposition to Complaint Counsel's Motion For Summary Decision," dated August 31, 2017 attached hereto.

[5] All references to "Statement of Disputed Facts" refer to "Respondent Impax Laboratories, Inc.'s Statement of Material Facts That Remain In Dispute" attached hereto.

(*Id.* ¶ 2.) [redacted]

[redacted] (*Id.* ¶ 4.)

The SLA: On June 8, 2010, Endo and Impax settled their litigation by signing a Settlement & License Agreement. (*See* CC's Statement of Undisputed Facts ¶ 18.) The SLA granted Impax a license to begin selling generic Opana ER no later than January 1, 2013, before Endo's patents-in-suit were to expire. (*Id.* ¶ 21.)

During settlement negotiations, Impax sought a license with the earliest possible guaranteed effective date. (Statement of Disputed Facts ¶¶ 1-4.) Endo steadfastly refused a date earlier than January 1, 2013. (*Id.* ¶ 6.) At the same time, Impax was aware that Endo had additional patents pending that if issued could cover generic Opana ER, and that Endo could acquire still other patents. (*See* Hassi Decl. Ex. AA, Impax_Opana_PartIII_0037996.) To ensure that Impax could in fact launch free from patent risk on January 1, 2013, Impax sought and obtained a license and covenant with respect to all patents that might otherwise block Impax from launching under the SLA. (Statement of Disputed Facts ¶ 7.) The SLA's broad patent license and covenant not to sue covered all relevant patents owned by Endo, both those existing and those acquired in the future. (*Id.*) The license allowed Impax to launch—and to stay on the market after launch—free from all patent litigation risk. (*Id.* ¶ 8.)

Impax sought other terms to ensure it would have the opportunity to compete in a robust market. Specifically, Impax was concerned that Endo may attempt to move sales away from its Opana ER to a new product or formulation. (*Id.* ¶ 16.) So it sought and obtained terms intended to incentivize Endo to continue supporting the existing Opana ER. (*Id.* ¶ 17.) Those terms encouraged Endo to grow its sales in return for a royalty, and discouraged Endo from degrading the opportunity with the threat of a payment to Impax under certain circumstances (the "Endo

Credit" term). (*Id*. ¶ 18.) The terms were contingent on numerous factors that were unknowable at the time they were negotiated, including peak and minimum Opana ER sales at future dates and Endo's ability to market a new product or formulation of Opana ER. (*Id*. ¶ 24.) What impact those terms would have in the future was unknown to both Impax and Endo, and neither company modeled the possible outcomes. (*Id.* ¶ 21.) But the possible future outcomes included (1) Impax paying Endo a royalty on the sales of its generic; (2) Endo paying Impax a penalty based on Endo's degradation of the generic opportunity; or (3) no payments changing hands at all. (*Id*. ¶¶ 22-24.)

During negotiations, however, Endo represented to Impax that it had no intention of discontinuing or limiting its support for Opana ER, either by switching the market to a reformulated version or otherwise. (*Id*. ¶ 15-16.) Impax consequently did not anticipate that it would be paid pursuant to the Endo Credit term. (*Id*. ¶ 19.) Endo likewise did not anticipate that it would make a payment to Impax under the Endo Credit term. (*Id*. ¶ 20.) The Endo Credit term, and the SLA more broadly, did not guarantee Impax would receive any payment from Endo. (*Id*. ¶ 22.) At the time the SLA was signed, Endo did not pay any money to Impax pursuant to that agreement. (*Id*. ¶ 23.) Years later, due to unforeseen events outside of Endo's and Impax's control, Endo made a payment to Impax pursuant to the Endo Credit term. (*Id*. ¶ 28.)

The SLA also contained a commitment from Endo that it would not sell an authorized generic version of Opana ER during Impax's 180-day exclusivity period (the "No AG" term), which [redacted] (*Id*. ¶ 29.) Endo never launched an authorized generic Opana ER. (*See* Hassi Decl. ¶ 15, IMS Sales Data,

Impax_Opana_PartIII_0000005 (showing no Endo sales of a generic oxymorphone ER product).).

The DCA: At the time Impax and Endo agreed to the SLA, they also signed a Development and Co-Promotion Agreement (the "DCA"). (CC's Statement of Undisputed Facts ¶ 20.) That agreement concerned a specific follow-on formulation of Rytary®, an Impax drug used to treat Parkinson's disease. (*Id.* ¶ 34.) The follow-on was known as IPX203, and both parties believed it would improve upon Rytary®. (*Id.*) Under the DCA, Endo contributed $10 million for the research and development of IPX203, a product Impax estimated would cost $[redacted] to develop. (*Id.* ¶¶ 34, 36.) Endo also committed to make additional contributions if Impax achieved certain research and development milestones. (CC's Statement of Undisputed Facts ¶ 27.) In exchange, Endo would promote the product to non-neurologists and retain all profits based on sales resulting from IPX203 prescriptions written by those doctors. (*Id.* ¶ 37.)

During Impax's extensive R&D work over a period of years, it determined that [redacted] (Statement of Disputed Facts ¶ 38.) [redacted] (*Id.*) [redacted] (*Id.* ¶ 39.) The companies consequently terminated the DCA in 2015. (*Id.*) Impax is pursuing the new IPX203 formulation, which could lead to an improved treatment for Parkinson's patients and is still a strategically important product candidate for the company. (*Id.* ¶ 40.) [redacted], Impax had devoted extensive time and resources to the IPX203

formulation as defined in the DCA, including significant labor hours, clinical studies, and research and development expenses, at a cost to Impax that far exceeds $[redacted] million. (*Id.* ¶ 41.)

Subsequent Patent Developments: Following settlement of the Endo-Impax patent litigation, Endo obtained an arsenal of additional patents covering Opana ER. (*See* CC's Statement of Undisputed Facts ¶¶ 30-34.) In 2012, for example, it acquired Patent No. 7,851,482 from Johnson Matthey (*See* Leefer Decl. Ex. HH at n.17), and received government approval of Patent Nos. 8,309,122 and 8,329,216. (*See* CC's Statement of Undisputed Facts ¶¶ 31-32.) In 2014, Endo received approval for Patent No. 8,808,737 and obtained Patent No. 8,871,779 from Mallinckrodt LLC. (*Id.* ¶ 34.) Endo filed infringement suits asserting these patents against a number of Opana ER ANDA holders, including all generic companies with which Endo had previously settled Opana ER patent infringement claims. (*See, e.g.*, Hassi Decl. Ex. L, Compl., *Endo Pharm. Inc. v. Par Pharm. Cod.*, No. 13-cv-3284 (S.D.N.Y. May 15, 2013); Hassi Decl. Ex. BB, Compl., *Endo Pharm. Inc. v. Actavis Inc.*, No. 12-cv-8985 (S.D.N.Y. Dec. 11, 2012)).

Endo's new patents have proven to be formidable barriers to the other ANDA filers. A district court in the Southern District of New York held that the ANDA holders infringed the '122 and '216 patents, and enjoined them from selling generic Opana ER. (Leefer Decl. Ex. II, *Endo Pharm. Inc. v. Amneal Pharm., LLC*, 2015 WL 9459823 (S.D.N.Y. Aug. 18, 2015)). A court in the District of Delaware similarly found that the '779 patent is valid and infringed. (Hassi Decl. Ex. K, Opinion, ECF No. 232, *Endo Pharm. Inc. v. Actavis Inc.*, No. 14-cv-1381-RGA (D. Del. Aug. 30, 2017); Leefer Decl. Ex. HH, *Endo Pharm. Inc. v. Amneal Pharm., LLC*, 224 F. Supp. 3d 368 (D. Del. 2016)). And the Federal Circuit concluded that Opana ER ANDA holders who had settled previous ANDA litigation with Endo not have an implied license to

Endo's patents. (Hassi Decl. Ex. CC, *Endo Pharm. Inc. v. Actavis Inc.*, 746 F.3d 1371, 1376-79 (Fed. Cir. 2014)).

Since early 2013, Impax has been the only company supplying generic Opana ER free from risk of an injunction or patent damages. (Statement of Disputed Facts ¶ 13.) Several other Opana ER ANDA filers obtained FDA approval, but did not launch their products at-risk in the face of Endo's patent portfolio. (*See* Hassi Decl. ¶15, IMS Sales Data, Impax_Opana_PartIII_0000005 (showing no sales for other Opana ER ANDA filers).) The one generic that has sold generic Opana ER at-risk, Actavis, has since been ordered from the market. (Leefer Decl. Ex. II, *Endo Pharm.*, 2015 WL 9459823, at 65-66.) By virtue of the SLA, Impax is the only Opana ER ANDA filer with the right to sell low-cost generic Opana ER. (Statement of Disputed Facts ¶ 12.) Even Endo stopped selling branded Opana ER: At the FDA's request, Endo has withdrawn its newer crush-resistant form of Opana ER. (*Id*. ¶ 14.) Thus, as of September 1, 2017, Impax will be the only source of branded or generic Opana ER (*id*.)—a fact that Complaint Counsel wants to exclude from the record and the Commission's rule-of-reason analysis.

B. Relevant Procedural Posture.

On April 5, 2017, Complaint Counsel served contention interrogatories that demanded Impax identify the factual bases for all procompetitive justifications underlying Defense No. 8. (Hassi Decl. Ex. A, Interrog. Nos. 2-3.) On June 1, 2017, Complaint Counsel moved to compel responses. (Hassi Decl. Ex. B, Mot. to Compel at 1, 3-5.) Complaint Counsel contended that it could not "conduct meaningful discovery," "prepare for trial," or otherwise determine whether "Impax can demonstrate legitimate, cognizable, procompetitive justifications" absent responses to its interrogatories. (*Id*.) Impax explained that it would be prejudicial to require answers to

contention interrogatories while discovery was ongoing and "the factual record [was] far from complete." (Leefer Decl. Ex. C, Mot. to Compel Opp. at 2, 4-8.)

Judge Chappell agreed with Impax. He denied Complaint Counsel's motion and held that Impax need not articulate the procompetitive justifications underlying Defense No. 8 until after the close of all discovery. Judge Chappell explained that "Complaint Counsel ha[d] not demonstrated that the contention interrogatories [were] ***capable*** of being answered at an earlier time than the close of discovery." *In re Impax Labs., Inc.*, 2017 WL 2570856, at *3 (F.T.C. June 12, 2007) (emphasis added). Discovery is currently ongoing, and Impax has not yet responded to Complaint Counsel's contention interrogatories. (Hassi Decl. Ex. C, Second Revised Scheduling Order.)

Complaint Counsel filed its Motion seeking summary decision with respect to Defense No. 8 on August 3, 2017.

III. LEGAL STANDARD

Under Commission Rule 3.24, summary decision is appropriate only when "there is no genuine issue as to any material fact regarding liability or relief." 16 C.F.R. § 3.24(a)(2). The party seeking summary decision "has the burden of establishing the nonexistence of any genuine issue of material fact, and all doubts are resolved against him." *In re Hearst Corp.*, 80 F.T.C. 1011, 1014 (1972). Rule 3.24 is construed consistent with Federal Rule of Civil Procedure 56. *In re Kroger Co.*, 98 F.T.C. 639, 726 (1981).

Summary decision should not be granted "before Respondents have had adequate time for discovery." *In re Nat. Organics, Inc.*, No. 9294, 2001 WL 1478367, at *2 (F.T.C. Jan. 30, 2001); *see Khan v. Parsons Glob. Servs., Ltd.*, 428 F.3d 1079, 1087 (D.C. Cir. 2005) ("a party opposing summary judgment needs a 'reasonable opportunity' to complete discovery before responding to a summary judgment motion").

IV. ARGUMENT

A. Complaint Counsel Cannot Escape its Burdens Under the Rule of Reason.

Under the rule of reason, the "plaintiff bears the initial burden of showing that an agreement had a substantially adverse effect on competition." *Buccaneer Energy (USA) Inc. v. Gunnison Energy Corp.*, 846 F.3d 1297, 1310 (10th Cir. 2017) (quotation omitted). Only if the plaintiff satisfies that obligation will "the burden shift[] to the defendant to come forward with evidence of the procompetitive virtues of the alleged wrongful conduct." *Id.*; *see O'Bannon v. NCAA*, 802 F.3d 1049, 1070 (9th Cir. 2015). Indeed, until "Plaintiffs carr[y] their initial burden . . . to show anticompetitive effects," the question whether a restraint "had pro-competitive effects" has "no bearing." *United States v. Am. Express Co.*, 838 F.3d 179, 205 (2d Cir. 2016) (quotation omitted).

Here, Complaint Counsel suggests that the "use of a large reverse payment to induce [a] generic to accept a settlement restricting its entry" is by its nature an "anticompetitive harm." (Mot. at 14.) Its premise is that any "alleged reverse payment [] creates the antitrust concern" and therefore "requires justification" by defendants. (*Id*. at 13.)

That premise was explicitly rejected by the Supreme Court in *Actavis*. There, the FTC urged the Court "to hold that reverse payment settlement agreements are presumptively unlawful and that courts reviewing such agreements should proceed via a 'quick look' approach, rather than applying a 'rule of reason.'" 133 S. Ct. at 2237. That approach would have "shift[ed] to a defendant the burden to show empirical evidence of procompetitive effects" any time the government identified a reverse-payment arrangement. *Id*. (quoting *Cal. Dental Ass'n v. FTC*, 526 U.S. 756, 775 n.12 (1999)). The Court rejected the FTC's approach since the "complexities" of reverse-payment settlements are such that "[t]he existence and degree of any anticompetitive

consequence may also vary" based on a payment's characteristics and "any other convincing justification." *Id*. Therefore, "the FTC must prove its case as in other rule-of-reason cases." *Id*.

This means that Complaint Counsel must demonstrate that there are "significant unjustified anticompetitive consequences" arising from the challenged reverse-payment arrangement. *Id*. at 2238. And until it does, Impax's potential (and as-of-yet unarticulated) procompetitive justifications are neither relevant nor "appropriate to weed out [as] legally insufficient defenses prior to trial." Mot. at 8; *see id*. ("***once*** the plaintiff meets its initial burden to show anticompetitive effects, the defendant must ***then*** show the challenged restraint promotes a legitimate procompetitive objective" (emphasis added)); *Am. Express*, 838 F.3d at 205 ("It was not [defendant's] burden to disprove anticompetitive effects; it was Plaintiffs' burden to prove them" in the first instance).

In sum, Complaint Counsel may not rely on any presumptions, quick-looks, or shortcuts. *Actavis*, 133 S. Ct. at 2237-38 (describing need for "proper analysis"); *In re Loestrin 24 Fe Antitrust Litig.*, 814 F.3d 538, 551 n.12 (1st Cir. 2016) (*Actavis* did not "overhaul the rule of reason"). Its task is a "fact intensive" one that is "not easy to resolve at the summary judgment stage." *In re Wellbutrin XL Antitrust Litig.*, __ F.3d __, 2017 WL 3531069, at *23 n.64 (3d Cir. Aug. 9, 2017).

B. Complaint Counsel's Motion Improperly Truncates the Rule of Reason.

1. There are No Artificial Limitations on Rule-of-Reason Analysis.

Complaint Counsel argues that the only considerations relevant in rule-of-reason cases are the "circumstances at the time the agreement was entered." (Mot. at 15; *see also id*. at 17.) It urges the Commission to (1) ignore actual effects and assess the competitive effects exclusively on "an *ex ante* basis," and (2) declare invalid any possible defenses touching on facts arising after Impax executed the purported reverse-payment settlement. (*Id*. at 15.) In so arguing,

Complaint Counsel seeks a departure from a century of rule-of-reason law. If its position is adopted by the Commission, it would represent a prescriptive regulation at odds with an entire canon of Supreme Court jurisprudence.

To begin, it is well-settled that plaintiffs in rule-of-reason cases must prove that a challenged restraint, "***as it actually operates in the market***, has unreasonably restrained competition." *Jefferson Par. Hosp. Dist. No. 2 v. Hyde*, 466 U.S. 2, 29 (1984) (emphasis added). This means that courts look to a challenged restraint's actual effects above all else, without limitations on the temporal scope of the evidence. *Copperweld Corp. v. Indep. Tube Corp.*, 467 U.S. 752, 768 (1984) (rule of reason is an inquiry into a restraint's "actual effect"); *United States v. Microsoft Corp.*, 253 F.3d 34, 95 (D.C. Cir. 2001) (per curiam) ("[P]laintiffs must show that [a defendant's] conduct unreasonably restrained competition. Meeting that burden 'involves an inquiry into the actual effect' of [the defendant's] conduct on competition" in the relevant market (quoting *Jefferson Parish*, 466 U.S. at 29)). As the Court emphasized in *Actavis*, the "basic question" is whether the restraint caused "significant unjustified anticompetitive consequences." 133 S. Ct. at 2238. And by definition, a "consequence" "***follows as an effect*** of something that came before." Black's Law Dictionary (10th ed. 2014) (emphasis added).

Indeed, the Supreme Court has never restricted the rule of reason to evidence from a particular time period. As it explained a century ago, the "true test of legality" in rule-of-reason cases focuses on "the facts peculiar to the business to which the restraint is applied; its condition ***before and after*** the restraint was imposed; [and] the nature of the restraint and its effect, ***actual or probable***." *Bd. of Trade of Chicago*, 246 U.S. at 238 (emphasis added); *see Cont'l T.V.*, 433 U.S. at 49 ("Under [the rule of reason], the factfinder weighs ***all of the circumstances of a case*** in deciding whether a restrictive practice should be prohibited as imposing an unreasonable

restraint on competition." (emphasis added)). The FTC and Department of Justice have long understood the need to "examine whether the agreement, if already in operation, has caused anticompetitive harm." FTC & DOJ, *Antitrust Guidelines for Collaborations Among Competitors* 4 (2000).[6]

Certainly, the Commission may look at intent and other issues existing at the time the purported restraint was imposed. Those factors "help the court to interpret facts and to ***predict*** consequences" otherwise unknown. *Bd. of Trade of Chicago*, 246 U.S. at 238 (emphasis added). But there is no reason to predict anything when the actual effects are known; when the actual effects of a restraint are plain, reality governs. *Board of Trade of Chicago* is instructive on this point. There, the district court improperly excluded evidence regarding the purpose and historical background of a purportedly unreasonable restraint. As the Supreme Court explained, however, the exclusion of *ex ante* evidence was harmless because the *ex post* record was clear: The purported restraint actually "helped to improve market conditions" and "had no appreciable effect on" competition. *Id*. at 238-41.

Board of Trade of Chicago is not alone in its focus on actual effects. Both courts and the Commission routinely rely on *ex post* evidence of competitive effects to assess whether a challenged restraint violated the antitrust laws. In *FTC v. Indiana Federation of Dentists*, 476 U.S. 447 (1986), for instance, the Commission found that defendants' conduct had the "actual effect of eliminating . . . competition among dentists and preventing insurers from obtaining access to x rays in the desired manner." *Id.* at 452. This finding turned on evidence of "actual detrimental effects" arising from post-restraint events. *Id*. at 452, 460-61 (evidence of post-restraint detrimental effects discharged Complaint Counsel's burden under the rule of reason);

[6] *Available at* https://www.ftc.gov/sites/default/files/documents/public_events/joint-venture-hearings-antitrust-guidelines-collaboration-among-competitors/ftcdojguidelines-2.pdf.

see In re Indiana Fed'n of Dentists, 101 F.T.C. 57, 73-79 (1983) (noting that "dental insurance companies were unable to obtain x-rays with the regularity and frequency they desired" and that "[w]ithin one year," some insurers experienced "a backlog of approximately 600 unpaid claims").

In *In re North Carolina Board of Dental Examiners*, 152 F.T.C. 640 (2011), the Commission similarly cited post-restraint evidence of actual "higher prices" and reduced consumer choice to support its rule-of-reason determination. *Id*. at 686-87 ("as a result of the Board's action . . . numerous non-dentist teeth whitening providers in North Carolina stopped offering teeth whitening services"). The Fourth Circuit and Supreme Court affirmed the Commission's decision. *N.C. Bd. of Dental Exam'rs v. FTC*, 717 F.3d 359, 374-75 (4th Cir. 2013), *aff'd*, 135 S. Ct. 1101 (2015).

And just as the Supreme Court did in *Board of Trade of Chicago*, lower courts regularly enter judgment for defendants when *ex ante* fears of competitive harm never materialize in practice. *See, e.g.*, *Tops Mkts., Inc. v. Quality Mkts., Inc.*, 142 F.3d 90, 96-97 (2d Cir. 1998) (affirming summary judgment for the defendant when plaintiff "failed to show any adverse effect on competition as a whole," despite evidence of "***potentially*** higher prices"); *Minebea Co. v. Papst*, 444 F. Supp. 2d 68, 219 (D.D.C. 2006) (judgment for defendants when, "even if Papst had intended to cause anticompetitive effects, none have actually occurred"); *Richter Concrete Corp. v. Hilltop Basic Res., Inc.*, 547 F. Supp. 893, 919 (S.D. Ohio 1981) ("The alleged anticompetitive effect . . . never materialized and does not exist. Absent any significant anticompetitive effect, the 1964 agreement is not an unreasonable restraint of trade, and does not violate Section 1.").[7]

[7] In *Actavis*, the Court looked at hypothetical effects because Complaint Counsel urged it to. 133 S. Ct. at 2234-35.

This approach—evaluating the actual effects of a restraint by looking to "all of the circumstances of [the] case," irrespective of timeframe, *Cont'l T.V.*, 433 U.S. at 49—is consistent with antitrust law generally. The Supreme Court "has long recognized that Congress intended to outlaw only unreasonable restraints" of trade when it enacted the Sherman Act. *State Oil*, 522 U.S. at 10; *see Leegin*, 551 U.S. at 885-86. Thus, while some restraints "have such predictable and pernicious anticompetitive effect, and such limited potential for procompetitive benefit, that they are deemed unlawful *per se*," *State Oil*, 522 U.S. at 10, the vast majority of restraints do not always harm competition and must be analyzed "in light of the ***real market forces at work***," *Leegin*, 551 U.S. at 886 (emphasis added).

Actavis' approach to reverse-payment settlements is no different. (Mot. at 15.) The Court was unequivocal: Reverse-payment settlements only "***sometimes*** violate the antitrust laws," and must therefore be evaluated "as in other rule-of-reason cases." 133 S. Ct. at 2227, 2237 (emphasis added). This includes evaluation of "the facts peculiar to the business to which the restraint is applied; its condition before and after the restraint was imposed; [and] the nature of the restraint and its effect, actual or probable." *Bd. of Trade of Chicago*, 246 U.S. at 238. No reverse-payment settlement is unlawful based on its existence at a moment in time. *Actavis*, 133 S. Ct. at 2237 (rejecting any anticompetitive presumptions).

Complaint Counsel cites a handful of cases for the ostensible proposition that competitive effects should be judged on an *ex ante* basis, and therefore that post-settlement rulings of patent validity are irrelevant. Complaint Counsel is wrong. There is no "general principle" that an agreement's competitive effects must be assessed *ex ante*. (Mot. at 15.)

All of the cases Complaint Counsel cites as support for its *ex ante* approach reference two decisions: *Polk Bros., Inc. v. Forest City Enterprises, Inc.*, 776 F.2d 185 (7th Cir. 1985), and

SCM Corp. v. Xerox Corp., 645 F.2d 1195 (2d Cir. 1981).[8] Both decisions are inapposite. *Polk Bros.* held that when determining whether an ***ancillary restraint*** should receive *per se* or rule of reason treatment, a court should evaluate conditions "at the time [the restraint] was adopted." 776 F.2d at 189. It says nothing about rule of reason itself—which the court may or may not apply to the ancillary restraint depending on the threshold determination.

In *SCM*, the defendants allegedly acquired a patent unlawfully, and then unilaterally refused to license that patent. 645 F.2d at 1202-03. The court held that if the patent was acquired lawfully, then the defendants' subsequent refusal to license was lawful, since refusal is "expressly permitted by the patent laws." *Id.* at 1204-07. The court's analysis necessarily hinged on whether the initial acquisition was lawful. *Id.* at 1206-07 ("analyzing the lawfulness of the acquisition of a patent necessitates that we primarily focus upon the circumstances of the acquiring party and the status of the relevant product and geographic markets at the time of acquisition"). The court did not address the rule-of-reason framework. *Id*.

Patent litigation outcomes are necessarily uncertain and often parties will settle in good faith years before a patent is determined to be invalid. It is understandable that a court would not credit the later finding of invalidity to judge the good faith settlement unlawful. Otherwise, good faith patent settlements would be discouraged. But that is a far cry from Complaint Counsel's

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[8] *See Valley Drug Co. v. Geneva Pharm., Inc.*, 344 F.3d 1294, 1306 (11th Cir. 2003) (citing *Polk Bros.* and *SCM Corp.*); *In re Cipro Cases I & II*, 348 P.3d 845, 870 (Cal. 2015) (citing *Valley Drug*, 344 F.3d at 1306); *Apotex, Inc. v. Cephalon, Inc.*, __ F. Supp. 3d. __, 2017 WL 2473148, at *5 (E.D. Pa. June 8, 2017) (citing *Valley Drug* and *In re Wellbutrin XL Antitrust Litig.*, 133 F. Supp. 3d 734, 753 (E.D. Pa. 2015), which in turn cites *Polk Bros.* and *SCM Corp.*).

The *Apotex* decision additionally cites *In re Lipitor Antitrust Litig.*, 46 F. Supp. 3d 523 (D.N.J. 2014), for the proposition that the value of an alleged reverse payment must be assessed "at the time of the settlement." *Id.* at 544. But whether economic valuation is done on an *ex ante* basis is distinct from the question whether anticompetitive effects actually occurred. *See, e.g.*, *Okerlund v. United States*, 365 F.3d 1044, 1053 (Fed. Cir. 2004) (economic valuation for tax purposes "must always be made as of the [transfer] date relying primarily on ex ante information").

argument here that a finding of patent validity, before the antitrust trial, should be excluded from the competitive effects analysis. While "later evidence of validity will not automatically demonstrate an agreement was procompetitive," *In re Cipro*, 348 P.3d at 870, the entire circumstances must be considered, "[i]f a patent were known to be valid, an agreement foreclosing competition no more than the statutory monopoly would not restrain trade beyond what federal law permitted." *Id*. at 856.

In re Aggrenox Antitrust Litigation, 94 F. Supp. 3d 224 (D. Conn. 2015), emphasizes this point and Complaint Counsel's citation to it is particularly misleading. (Mot. at 16.) Complaint Counsel omits a critical qualifying phrase from the quoted sentence, which reads in full: "The salient question is not whether the fully-litigated patent would ultimately be found valid or invalid—***that may never be known***—but whether the settlement included a large and unjustified reverse payment leading to the inference of profit-sharing to avoid the risk of competition." *Aggrenox*, 94 F. Supp. 3d at 241 (emphasis added). Patent validity may not be known at the time of trial in the typical case. But when patent validity ***is*** known, as it is with respect to four of the subsequently issued patents covered by the SLA, it is relevant to the effects analysis. Indeed, as the *Aggrenox* court recognized in a subsequent decision, the relevant question under *Actavis* is whether the challenged settlement "effectively extend[ed] the life of the patent beyond its expected life in the absence of settlement." *In re Aggrenox Antitrust Litig.*, 2015 WL 4459607, at *10 (D. Conn. July 21, 2015).

At bottom, the Commission cannot prospectively exclude facts that are at odds with Complaint Counsel's constrained worldview. Evidence of actual effects go to the "heart of this case." (Hassi Decl. Ex. B, Mot. to Compel at 1.) The rule of reason demands consideration of all relevant evidence, both before and after a restraint is imposed. *Bd. of Trade of Chicago*, 246

U.S. at 238; *King Drug Co. of Florence, Inc. v. SmithKline Beecham Corp.*, 791 F.3d 388, 398 n.15 (3d Cir. 2015) (reverse-payment claims are subject to "traditional, full-fledged rule of reason standard").

Any other approach would overturn principles that have guided rule-of-reason analysis since the Supreme Court first articulated the test a century ago. It would also elevate ***hypothetical*** competitive effects over ***known*** competitive impact. Neither law nor logic permits such a result, especially when Complaint Counsel is using its Motion as a poorly-disguised motion in limine, seeking to exclude evidence that undisputedly demonstrates the SLA achieved procompetitive benefits. *Cal. Dental*, 526 U.S. at 774-78 & n.12 (reversing grant of summary judgment; stressing need for empirically-rigorous evidence regarding anticompetitive effects because "assumption alone will not do"); *Roy B. Taylor Sales, Inc. v. Hollymatic Corp.*, 28 F.3d 1379, 1385 (5th Cir. 1994) ("Speculation about anticompetitive effects is not enough."); *Green v. Teddie Kossof Salon & Day Spa*, 2017 WL 3168995, at *4 (N.D. Ill. July 26, 2017) (using a motion for partial summary judgment as "a motion in limine in disguise" is "not a proper" tactic).

2. Alleging "Elimination of Risk" Does Not Satisfy Complaint Counsel's Initial Burden to Show Adverse Competitive Effects.

Complaint Counsel contends that the only "antitrust inquiry" in this case is "whether the payment seeks to prevent the risk of competition, which itself constitutes the relevant anticompetitive harm." (Mot. at 10 (citing *Actavis*, 133 S. Ct. at 2236).) It argues that any time a reverse-payment settlement avoids some "risk of competition," no matter how insignificant or unlikely, anticompetitive harm exists. *Id*. at 18; *see also* Brief of FTC as Amicus Curiae in Support of No Party at 17-18, *In re Wellbutrin XL Antitrust Litig.* (3d Cir. Mar. 11, 2016) ("*Wellbutrin* Br.") (asserting there is no need to analyze "what actually would have occurred in

the market absent the anticompetitive conduct," and that a settlement may violate antitrust laws "whether or not … competition would have ultimately materialized" in its absence). By its telling, Complaint Counsel need not prove that a reverse-payment settlement actually delayed generic competition or resulted in any actual harm to consumers. Mot. at 17; *see Wellbutrin* Br. at 16 n.7.

Complaint Counsel's suggested approach misstates the law and, if adopted, would turn antitrust law on its head. The Supreme Court has concluded that reverse-payment settlements only "sometimes unreasonably diminish competition in violation of the antitrust laws." *Actavis*, 133 S. Ct. at 2227. Thus, as with other contractual restraints evaluated under the rule of reason, reverse-payment settlements must be assessed with reference to "all of the circumstances of a case" to decide "whether [the] restrictive practice should be prohibited as imposing an ***unreasonable*** restraint on competition." *Cont'l T.V.*, 433 U.S. at 49 (emphasis added); *Actavis*, 133 S. Ct. at 2237 (reverse-payment settlements reviewed "as in other rule-of-reason cases").

But Complaint Counsel eschews this holistic evaluation of restraints. It wants to limit its *prima facie* burden to establishing a settlement restrained potential competition in any way, i.e. eliminated any risk. But every Hatch-Waxman settlement eliminates risk. There is ***always*** a possibility that a patent will be held invalid, unenforceable, or not infringed, meaning settlements always eliminate that risk of potential competition. Moreover, accurate or not, patent holders typically harbor some concern that a generic will enter at-risk; any settlement with the generic eliminates that risk. And even a settlement that grants a purported infringer a license with no restrictions—allowing immediate market entry—the settlement would still eliminate the risk of competition from ***other*** ANDA filers. *Actavis*, 133 S. Ct. at 2235 ("litigation victory will free not just the challenger to compete, but all other potential competitors too"); *Gen. Protecht Grp.,*

Inc. v. Leviton Mfg. Co., 2012 WL 1684573, at *29 (D.N.M. May 12, 2012) ("When a court declares a patent invalid, the patent holder can never enforce that patent against anyone again—both the parties to the case and anyone else who might be accused of infringement—under issue-preclusion principles." (citing *Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found.*, 402 U.S. 313, 334 (1971))). Complaint Counsel's "elimination of risk" test captures every patent litigation settlement.

Complaint Counsel consequently suggests replacing a thorough, fact-intensive inquiry regarding competitive effects with an inquiry that conclusively deems anticompetitive any patent settlement like the SLA. But the law is clear: Simply establishing that a settlement agreement restrained competition is not enough to meet Complaint Counsel's burden under the rule of reason, it never has been. *Bd. of Trade of Chicago*, 246 U.S. at 238; *Standard Oil Co. v. United States*, 221 U.S. 1, 60 (1911).

Indeed, all contracts restrain trade—"[t]o bind, to restrain, is of their very essence." *Bd. of Trade of Chicago*, 246 U.S. at 238. Yet "the legality of an agreement or regulation cannot be determined by so simple a test, as whether it restrains competition." *Id.* To do so would mean that "every conceivable contract or combination which could be made concerning trade or commerce . . . anywhere in the whole field of human activity [is] illegal." *Standard Oil*, 221 U.S. at 60. That is not what the antitrust laws intend. *Am. Needle, Inc. v. Nat'l Football League*, 560 U.S. 183, 190 (2010). And it is not how the Supreme Court evaluates contractual restraints. The Court has never rigidly and literally applied the Sherman Act's reference to "restraint[s] of trade." 15 U.S.C. § 1. Rather, it assesses a purported restraint's actual competitive effects. *Bd. of Trade of Chicago*, 246 U.S. at 238; *see Texaco Inc. v. Dagher*, 547 U.S. 1, 5 (2006) (disclaiming a literal approach to prohibitions against restraints of competition).

Actavis does not treat reverse-payment settlements differently. That case addressed the question whether reverse-payment settlements are immune from antitrust scrutiny under the scope-of-the-patent test. It concluded they are not. 133 S. Ct. at 2234-37 ("five sets of considerations lead us to conclude that the FTC should have been given the opportunity to prove its antitrust claim. . . . [and] that the FTC must prove its case as in other rule-of-reason cases").

At the time, lower courts feared that reverse-payment cases would prove administratively unfeasible absent some presumption regarding legality, lest patent mini-trials dominate the cases. *Actavis*, 133 S. Ct. at 2234. The *Actavis* Court rejected that concern, explaining that when there is a large and unexplained payment in a patent-litigation settlement agreement, the patent holder "likely" intends to restrict competition that a valid patent would otherwise prohibit: An "unexplained large reverse payment itself would normally suggest that the patentee has serious doubts about the patent's survival" and "can provide a workable surrogate for a patent's weakness." *Id*. at 2236-37. Accordingly, large and unexplained payments suggest that a patent holder "likely seeks to prevent the risk of competition" that it otherwise could not bar, rendering the need for patent mini-trials moot. *Id*. at 2236-37.

The only point the Supreme Court made by referencing elimination of risk was that traditional antitrust analysis under the rule of reason is appropriate even though patents are involved. *Id*. at 2234-37 (noting various possible competitive harms that justify traditional rule-of-reason analysis in reverse-payment cases); *In re Loestrin*, 814 F.3d at 544, 551 n.12 (*Actavis* "determined that 'five sets of considerations' weighed in favor of subjecting reverse payment settlements to antitrust scrutiny" rather than a presumption in either direction, but did not "overhaul the rule of reason"). Put differently, to "survive a motion to dismiss when raising an antitrust violation under *Actavis*, plaintiffs must allege facts sufficient to support the legal

conclusion that the settlement at issue involves a large and unjustified reverse payment" such that the Court can infer the existence of a weak patent. *In re Lipitor Antitrust Litig.*, __ F.3d __, 2017 WL 3585180, at *11 (3d Cir. Aug. 21, 2017) (quotation omitted). "If plaintiffs do so, they may proceed to prove their allegations ***under the traditional antitrust rule-of-reason analysis***." *Id*. (emphasis added; citing *Actavis*, 133 S. Ct. at 2237). *Actavis* stands for nothing more.

The Commission's decision in *In re McWane, Inc.*, No. 9351, 2014 WL 556261 (F.T.C. Jan. 30, 2014), is instructive. There, Complaint Counsel alleged that when "McWane saw that Sigma was preparing to enter the domestic fittings market," it "sought to ***eliminate the risk of competition*** by inducing Sigma to become an exclusive distributor of McWane's domestic fittings." *Id*. at *32 (emphasis added). McWane and Sigma's Master Distribution Agreement ("MDA") allegedly violated Section 1 by removing the risk that Sigma would independently enter the market in competition with McWane. *Id*. at *1-3, 32. Under Complaint Counsel's view of the law, the Commission's analysis should have stopped there. It did not. The Commission went on to evaluate whether, "but for the MDA, Sigma was sufficiently likely to enter the domestic fittings market to be considered a potential competitor of McWane." *Id*. at *32. The Commission found that, despite "troubling evidence" that "McWane entered the MDA in order to eliminate [the] possibility" of Sigma's independent entry, Sigma ultimately was not likely to have entered but for the MDA, rendering it "unlikely" that the MDA "had an anticompetitive effect." *Id*. at *32-37 (concluding under the rule of reason that the MDA's prohibition against Sigma independently producing domestic fittings "was unlikely to have had an anticompetitive effect" since "Sigma was not a probable entrant in the domestic fittings market"). The Commission subsequently upheld the MDA under the FTC Act. *Id*. at *37.

The mere fact that an agreement restrains some potential future competition—i.e., eliminates some risk—does not satisfy Complaint Counsel's burden to show competitive effects under the rule of reason.

C. Complaint Counsel's Attacks on Specific Procompetitive Justifications Fail.

Throughout its Motion, Complaint Counsel shadowboxes with "essentially three procompetitive justifications" (Mot. at 6.): (1) the SLA "allow[ed] generic entry before the expiration of Endo's patents" (*id*. at 10); (2) the "benefits of settlement" aided competition (*id.* at 12); and (3) the patent license in the SLA allowed Impax to remain on the market despite "Endo's success in enforcing some of its later-acquired patents" (*id.* at 7, 15).

In reality, each of these undeniable facts underscores the SLA's actual procompetitive benefits: The agreement facilitated five years (and counting) of unfettered, continuous generic Opana ER sales that would not have been possible otherwise. Because of the SLA, these sales have not been and can never be interrupted by ***any*** patent litigation.[9] Each of these facts therefore is relevant to traditional rule-of-reason analysis. They are evidence of procompetitive effects and thus "legally cognizable defenses under *Actavis*." (Mot. at 1.) The Motion must be denied for this reason as well.

1. Entry Before Patent Expiration is Procompetitive.

Complaint Counsel contends that any claim that a "settlement is procompetitive because it allows generic entry before the expiration of [relevant] patents directly conflicts with *Actavis*." (Mot. at 10.) This simply is not true. The Supreme Court is clear that entry before a patent expires is procompetitive and must be taken into account under the rule of reason: "We concede

[9] In particular, Impax has long-argued that not settling with Endo—and continuing to litigate Endo's patents—would have delayed Impax's market entry far beyond January 2013, even if Impax ultimately succeeded in invalidating Endo's patents or proving non-infringement. (Hassi Decl. Ex. D, Impax White Paper at 1, 20, 30, 35-36.)

that settlement on terms permitting the patent challenger to enter the market before the patent expires would also bring about competition, again to the consumer's benefit." *Actavis*, 133 S. Ct. at 2234.

2. All Benefits Arising from the Purported Reverse-Payment Settlement are Relevant.

Complaint Counsel claims that "*Actavis* rejected the argument that the benefits of settlement should render lawful the use of reverse payments in settlement." (Mot. at 12.) Relatedly, Complaint Counsel suggests that the only relevant consideration under the rule of reason is the purported reverse payment, discounting entirely any benefits flowing from the SLA as a whole. (*Id*. at 13-14.) This argument would eliminate from consideration, for example, evidence that Impax is now the only seller of Opana ER and the only reason consumers continue to have access to the product. The Commission cannot ignore this reality.

As previously noted, *Actavis* did not "overhaul the rule of reason." *In re Loestrin*, 814 F.3d at 551 n.12. It requires application of the traditional rule-of-reason analysis, which includes consideration of all procompetitive justifications related to the purported restraint. *Bd. of Trade of Chicago*, 246 U.S. at 238. In fact, the Court in *Actavis* explained that "offsetting or redeeming virtues are sometimes present" in reverse-payment agreements. 133 S. Ct. at 2236 ("[T]he parties may have provided for a reverse payment without having sought or brought about the anticompetitive consequences."). This means that an "antitrust defendant may show in the antitrust proceeding that legitimate justifications are present, thereby explaining the presence of the challenged term and showing the lawfulness of that term under the rule of reason." *Id*. (citing *Ind. Fed'n of Dentists*, 476 U.S. at 459).

There are no limitations on the benefits that can be considered, or from where in the settlement agreement they may flow. *Major League Baseball Props., Inc. v. Salvino, Inc.*, 542

F.3d 290, 338 (2d Cir. 2008) (Sotomayor, J., concurring) (undertakings "are typically evaluated as a whole under the rule of reason because the competitive effects of individual restraint are intertwined with the effects of the remainder of the venture"); *In re Wellbutrin*, 133 F. Supp. 3d at 753 ("The Court will evaluate the settlement as a whole, and not in a piecemeal, provision-by-provision approach.").

In *Indiana Federation of Dentists*, for example, the Court considered all purported benefits and justifications arising from the alleged restraint. This included both "countervailing procompetitive virtue[s]" found in the federation agreement (from which the challenged policy arose) as well as all other arguments that, "notwithstanding [the restraint's] lack of competitive virtue, the Federation's policy . . . should not be deemed an unreasonable restraint of trade." 476 U.S. at 459-63. The Commission should do the same.

3. *Actavis* Requires the Commission to Consider Patent-Related Defenses under the Rule of Reason.

Finally, Complaint Counsel contends that Impax cannot argue that decisions upholding Endo's patents as valid and infringed "justify" the SLA. (Mot. at 15.) The point, however, is that the SLA allowed Impax to provide consumers sustained generic supply in the face of numerous, valid additional patents. Absent the SLA, Impax would have been blocked from selling to those consumers, regardless of the outcome of its initial patent litigation with Endo. And even if Impax were hypothetically to prevail in any particular patent litigation, Impax would have been tied up litigating with Endo until well after January 2013—just as other ANDA filers have been. Thus, without the SLA, Impax would have supplied far less generic Opana ER to consumers—if it sold any at all. The patents at issue in Impax's underlying litigation with Endo have long since expired, but today no other ANDA filer is marketing generic Opana ER because Endo has deployed a bulwark of patents to which the SLA gave Impax a license. Of course, that

Endo's patents have been upheld—and that other generic companies have been enjoined from selling generic Opana ER—underscores how the SLA was a net positive for competition and consumers.

In any event, Complaint Counsel's argument ignores the unambiguous language in *Actavis*, which begins with the premise that a "'***valid*** patent excludes all except its owner from the use of a protected process or product,'" and that this lawful exclusion "may permit the patent owner to charge a higher-than-competitive price for the patented product." 133 S. Ct. at 2231 (quoting *United States v. Line Material Co.*, 333 U.S. 287, 308 (1948)). The problem with the scope-of-the-patent test, the Court reasoned, was that it simply ***assumed*** patent validity, when the patent at issue "may or may not be valid." *Id*. at 2231. Answering the "antitrust question" posed by a reverse-payment settlement requires consideration of "traditional antitrust factors"—including "potentially offsetting legal considerations present in the circumstances, ***such as . . . those related to patents***." *Id*. (emphasis added). Part of the purpose of that analysis is to determine whether the challenged settlement "lies beyond the limits of the patent monopoly." *Id.* at 2231-32. Complaint Counsel ignores this point entirely.

Complaint Counsel also ignores the fact that the Court was assessing whether reverse-payment settlements necessitate a "time consuming, complex, and expensive" inquiry regarding patent merits in antitrust cases. *Id.* at 2234. It was in that context that the Court concluded that litigating patent validity is "normally not necessary"—***not*** because patent validity is irrelevant to the analysis, but rather because payment size may be a "workable surrogate for a patent's

weakness." *Id*. at 2236-37.[10] That suggested "surrogate" only confirms the continuing importance of patent validity in the rule-of-reason framework.[11]

Where, as here, there is direct evidence of patent validity—such as court decisions upholding patents—nothing in *Actavis* precludes defendants from using that evidence to show that an alleged reverse-payment settlement did not "delay competition ***for longer than the patent's strength would otherwise permit***." *King Drug*, 791 F.3d at 409 (emphasis added); *see Aggrenox*, 2015 WL 4459607, at *10 (benchmark for measuring anticompetitive effects is "[the patent's] expected life had enforcement been sought'" (quoting *In re Cipro Cases I & II*, 348 P.3d at 864)).[12]

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[10] *But see In re Wellbutrin*, 2017 WL 3531069, at *21-22 (explaining that "risk aversion makes it difficult to use the size of a settlement as a proxy for the brand-name's likelihood of success in litigation," and noting that payment size is "far from dispositive" when it comes to assessing patent strength).

[11] This is not the first time the Supreme Court has endorsed a "surrogate" form of proof under the rule of reason. In *FTC v. Indiana Federation of Dentists*, the Court stated that proof of market power may serve as a "surrogate for detrimental effects." 476 U.S. at 461. But as that case itself shows, "surrogate" forms of proof remain subject to direct evidence. *See id*. at 460-61 (direct proof of "actual, sustained adverse effects on competition" obviated the need to rely on the "surrogate" of market power). Even if a defendant has market power, the defendant can counter that "surrogate" with direct evidence that its conduct "actually has a procompetitive effect on balance." *Agnew v. NCAA*, 683 F.3d 328, 335-36 (7th Cir. 2012).

[12] In *Cipro*, the California Supreme Court held that under the Cartwright Act, patent strength should be evaluated prospectively in order to determine "the average level of competition that would have obtained absent settlement": "Consider a patent with a 50 percent chance of being upheld. After litigation, on average, consumers would be subject to a monopoly for half the remaining life of the patent. A settlement that allowed a generic market entry at the midpoint of the time remaining until expiration would replicate the expected level of competition; the period of exclusion would reflect the patent's strength. But a settlement that delayed entry still longer would extend the elimination of competition beyond what the patent's strength warranted; to the extent it did, the additional elimination of the possibility of competition would constitute cognizable anticompetitive harm." 348 P.3d at 864; *see also id*. at 870 ("the relevant baseline is the average period of competition that would have obtained in the absence of settlement"). This approach may explain the Court's statement that post-settlement patent decisions do not bear on the settlement's legality under California law. *See id*. at 870.

While Impax's defense of the SLA does not hinge on post-settlement patent rulings, there is no basis in *Actavis* for preventing Impax from relying on evidence of patent strength. *See FTC v. Cephalon, Inc.*, 36 F. Supp. 3d 527, 531 (E.D. Pa. 2014) (expressing "doubt" that the FTC's position—"that there is simply no room for a defense based on the strength of the patent"—is "the most accurate reading of *Actavis*"). And contrary to Complaint Counsel's suggestion (Mot. at 11), admitting patent validity evidence is not a "repackaging" of the scope-of-the-patent test. The problem with the scope-of-the-patent test was that it presumed patent validity. *Actavis*, 133 S. Ct. at 2231. Here, Impax is not relying on a ***presumption*** of validity. It is relying on an actual ***adjudication*** of validity.

V. CONCLUSION

The Supreme Court in *Actavis* ruled that "the FTC must prove its case as in other rule-of-reason cases." *Id*. at 2237. If Complaint Counsel can meet its initial burden of demonstrating competitive effects under the rule of reason, it can argue that Impax's procompetitive-benefits evidence does not outweigh whatever harm Complaint Counsel can muster. But Complaint Counsel's Motion should be seen for what it is, a motion in limine seeking to avoid inconvenient evidence that it would prefer not to confront under a full rule-of-reason analysis. For the foregoing reasons, Complaint Counsel's Motion for Partial Summary Decision should be denied.

In contrast to the *Cipro* Court, Complaint Counsel rejects the notion that it must prove actual anti-competitive effects and denies that patent validity plays ***any*** role in the antitrust analysis.

Dated: August 31, 2017

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CERTIFICATE OF SERVICE

I hereby certify that on August 31, 2017, I filed the foregoing document using the FTC's E-Filing System, which will send notification of such filing to:

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CERTIFICATE FOR ELECTRONIC FILING

I hereby certify that the electronic copy sent to the Secretary of the Commission is a true and correct copy of the paper original and that I possess a paper original of the signed document that is available for review by the parties and the adjudicator.

DATED: August 31, 2017

/s/ *Anna M. Fabish*
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Notice of Electronic Service

I hereby certify that on September 08, 2017, I filed an electronic copy of the foregoing Respondent Impax Laboratories, Inc.'s Memoradum Of Law In Opposition To Complaint Counsel's Motion For Partial Summary Decision, Respondent Impax Laboratories, Inc.'s Statement Of Material Facts That Remain In Dispute, Declaration Of Edward D. Hassi In Support Of Respondent Impax Laboratories, Inc.'s Opposition To Complaint Counsel's Motion For Summary Decision, with:

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Complaint

I hereby certify that on September 08, 2017, I served via other means, as provided in 4.4(b) of the foregoing Respondent Impax Laboratories, Inc.'s Memoradum Of Law In Opposition To Complaint Counsel's Motion For Partial Summary Decision, Respondent Impax Laboratories, Inc.'s Statement Of Material Facts That Remain In Dispute, Declaration Of Edward D. Hassi In Support Of Respondent Impax Laboratories, Inc.'s Opposition To Complaint Counsel's Motion For Summary Decision, upon:

Markus Meier
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Complaint

Eileen Brogan
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UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

In the Matter of:	
IMPAX LABORATORIES, INC., a corporation.	**Docket No. 9373**

RESPONDENT IMPAX LABORATORIES, INC.'S STATEMENT OF MATERIAL FACTS THAT REMAIN IN DISPUTE

Pursuant to Rule 3.24, in support of its Opposition to Complaint Counsel's Motion for Partial Summary Decision, Respondent submits the following non-exhaustive statement of facts that remain in dispute and are material to Impax's Affirmative Defense No. 8.

Impax disputes the accuracy of only one of the facts listed in Complaint Counsel's Statement of Undisputed Facts.[1] However, Impax disputes that the body of facts contained in Complaint Counsel's Statement reflect all facts material to (i) Complaint Counsel's Motion for Partial Summary Decision, (ii) the rule-of-reason analysis reflected in Impax's Defense No. 8, or (iii) the interpretation of Defense No. 8 generally. Indeed, many of the facts included in Complaint Counsel's Statement are not material to any of these issues.

Procompetitive Effects of the Settlement & License Agreement ("SLA"):

1. Absent settlement, Impax would not have launched its generic Opana ER product[2] "at-risk."[3]

[1] Specifically, Impax disputes paragraph 10 in Complaint Counsel's statement, to the extent that it characterizes the representations Impax made in its Paragraph IV certification for the '250, '933, and '456 patents as "attesting that Impax's product did not infringe the patents and/or that the patents were invalid." Impax's Paragraph IV certifications speak for themselves. *See* IMPAX-OPANA-CID00000017 (Aug. 31, 2017 Declaration of Edward D. Hassi, Exhibit E); IMPAX-OPANA-CID00000019 (Hassi Decl. Ex. F).

[2] The term "generic Opana ER" in this Statement refers to generic versions of the original Opana ER formulation, not of Endo's allegedly crush-resistant reformulation. Generic or branded versions of reformulated Opana ER are identified as such.

[3] *See* Compl., *In re Impax Labs., Inc.*, Dkt. 9373 (Jan. 19, 2017) (Aug. 3, 2017 Declaration of Nicholas Leefer, Exhibit A) ¶ 41, Answer, *In re Impax Labs., Inc.*, Dkt. 9373 (Feb. 7, 2017) (Leefer Decl. Ex. B) ¶ 41; *see also*

2. Impax management never recommended Impax launch generic Opana ER "at-risk."[4]

3. For Impax to launch a generic product "at risk" it would need to have the approval of its Board of Directors.[5]

4. The Impax Board of Directors was never asked to approve, and never approved, a launch of generic Opana ER "at-risk."[6]

5. In the patent infringement suit between Endo Pharmaceuticals, Inc. ("Endo") and Impax settled by the SLA (the "Original Patent Litigation"), the court ruled for Endo on claim construction issues.[7]

6. When Impax negotiated a settlement with Endo, it negotiated for and obtained a license with the earliest guaranteed effective entry date Impax could extract from Endo. Endo would not have agreed to a settlement including a license with a guaranteed effective entry date any earlier than January 1, 2013.[8]

7. To ensure that Impax could in fact launch free from patent risk on the guaranteed license effective entry date of January 1, 2013, Impax sought and obtained license to any subsequently issued or obtained patents that might otherwise block Impax from launching under the terms of its settlement.[9] Impax successfully negotiated a broad patent license and covenant not to sue in the SLA that covered all relevant patents owned by Endo, both those existing and those acquired in the future.[10]

8. The SLA permitted Impax to sell generic Opana ER without fear of any additional patent infringement litigation with Endo regarding Impax's generic Opana ER product, and to

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Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories (Leefer Decl. Ex. BB), at 18-19.

[4] Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories, at 19 (Leefer Decl. Ex. BB); Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Third Set of Interrogatories, at 17 (Hassi Decl. Ex. G).

[5] Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories, at 10 (Leefer Decl. Ex. BB).

[6] *Id.* at 19.

[7] Order on Claim Construction, Dkt. 188, No. 09-831 (KSH) (D.N.J. Mar. 30, 2010) (Hassi Decl. Ex. H).

[8] Koch Deposition Trans. (dated 6/6/2017) 67:7-14 (Hassi Decl. Ex. I).

[9] IMPAX-OPANA-CID00007034–57 (Hassi Decl. Ex. J).

[10] *Id.*

specifically avoid litigation regarding Impax's generic Opana ER product[11] in *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC,* Case No. 12-cv-08115 (S.D.N.Y.), and *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*, Case No. 14-cv-01382 (D. Del.). [12]

9. The District Court's ruling in *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals*, LLC, 2015 WL 9459823 (S.D.N.Y. Aug. 18, 2015), regarding Endo's U.S. Patent Nos. 8,309,122 and 8,329,216 would have prevented Impax from marketing its generic Opana ER product, but for the SLA.[13]

10. The SLA permitted Impax to launch 10 years before the expiration of Endo's U.S. Patent Nos. 8,309,122 and 8,329,216—which Endo has since successfully asserted to enjoin all other Opana ER ANDA filers from marketing a generic original or reformulated Opana ER product—and to stay on the market without the threat of injunction or patent damages liability.[14]

11. The SLA permitted Impax to launch 16 years before the expiration of Endo's U.S. Patent No. 8,871,779—which a district court in the District of Delaware upheld as valid in Endo's patent litigation suits against other original and reformulated Opana ER ANDA filers—and to stay on the market without the threat of injunction or patent damages liability.[15]

12. The rights Impax obtained in the SLA have permitted Impax to sell generic Opana ER when all other ANDA filers have been prevented from doing so. Impax is the only company currently selling generic Opana ER.

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[11] Impax's generic version of Endo's reformulated Opana ER product, which Impax developed after the SLA and was not covered by the SLA, was the subject of these litigations.

[12] *See* Trial Opinion, *Endo Pharmaceuticals Inc. v. Actavis, Inc.*, No. 14-cv-1381-RGA (D. Del., Aug. 30, 2017), ECF No. 232 (Hassi Decl. Ex. K); *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*, 2015 WL 9459823 (S.D.N.Y. Aug. 18, 2015) (Leefer Decl. Ex. II).

[13] Complaint Counsel objects to the relevance of these patent rulings because they relate to patents that had not been issued at the time of the SLA and to judicial decisions that came over five years after the execution of the SLA. Complaint Counsel's Responses to Impax's First Set of Requests for Admission, at 5 (Hassi Decl. Ex. M); *but see* Mot. for Summary Decision, *In re Impax Labs., Inc.*, Dkt. 9373 (August 3, 2017), Complaint Counsel's Statement of Undisputed Facts ¶¶ 34, 36. This illuminates the misunderstanding that spurs this Motion. The fact that the SLA permitted Impax to market generic Opana ER despite such later-in-time patents and litigation is central to the rule-of-reason analysis of the restraint in question and its procompetitive effects.

[14] Denied in Complaint Counsel's Responses to Impax's First set of Requests for Admission (Hassi Decl. Ex. M), at 2.

[15] *See* Trial Opinion, *Endo Pharmaceuticals Inc. et al. v. Actavis, Inc. et al.*, No. 14-cv-1381-RGA, ECF No. 232 (D. Del. Aug. 30, 2017) (Hassi Decl. Ex. K).

13. Since early 2013, Impax has been the only company supplying generic Opana ER without risk of patent damages liability or injunction.[16] Several other Opana ER ANDA filers obtained FDA approval, but did not launch their products at-risk in the face of Endo's patent portfolio.[17]

14. Endo has agreed to comply with an FDA request to withdraw its reformulated Opana ER from the market. As of September 1, 2017, Impax's generic Opana ER will be the only FDA-approved form of oxymorphone ER available to consumers in branded or generic form.[18]

Alleged Payment Terms:

15. At the time Impax and Endo executed the SLA, Impax did not know that Endo would degrade the generic Opana ER opportunity, and during SLA negotiations, Endo represented to Impax that it had no intention of discontinuing or limiting its support for Opana ER.[19]

16. At the time Impax and Endo executed the SLA, Impax was concerned that Endo might attempt to move sales away from its Opana ER product to a new product or formulation.[20]

17. Impax negotiated the Endo Credit and contingent royalty terms in the SLA as incentives to encourage Endo to continue to support original Opana ER. [21]

18. Impax intended the Endo Credit and contingent royalty terms to incentivize Endo to continue to support original Opana ER.[22]

19. Impax did not anticipate or expect to be paid pursuant to the Endo Credit term.

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[16] IMS Sales Data, Impax_Opana_PartIII_0000005 (Hassi Decl. ¶ 15).

[17] *Id.*; FDA Orange Book (Hassi Decl. Ex. N).

[18] Complaint Counsel states that it does not have enough information to either admit or deny this fact. Complaint Counsel's Responses to Impax's First Set of Requests for Admission, at 3 (Hassi Decl. Ex. M). Although this fact remains in dispute, this information should be available to Complaint Counsel in a matter of weeks.

[19] Snowden Deposition Trans. (dated 8/2/2017) 114:3-6 (Hassi Decl. Ex. O).

[20] IMPAX-OPANA-CID000019449-50 (Hassi Decl. Ex. P); IMPAX-OPANA-CID00012004 (Hassi Decl. Ex. Q).

[21] Snowden Deposition Trans. (dated 8/2/2017) 114:3-115:4 (Hassi Decl. Ex. O).

[22] Snowden Deposition Trans. (dated 8/2/2017) 120:14-17 (Hassi Decl. Ex. O).

20. Endo did not anticipate or expect to make a payment to Impax under the Endo Credit term.[23]

21. Neither Impax nor Endo modeled the possible outcomes from the Endo Credit.[24]

22. The Endo Credit term, and the SLA more broadly, did not guarantee Impax would receive any payment from Endo.[25]

23. At the time the SLA was signed, Endo did not pay any money to Impax pursuant to the SLA.[26]

24. At the time the SLA was signed, whether either party would owe any payments to the other under the Endo Credit or royalty terms, and in what amount, was uncertain and depended on factors entirely outside of Impax's control.[27]

25. At the time Impax and Endo executed the SLA, one possible outcome of the Endo Credit and royalty terms was that Impax would be required to make a net payment to Endo.[28]

26. At the time Impax and Endo executed the SLA, one possible outcome of the Endo Credit term was that Endo could stop marketing original Opana ER before January 1, 2013, but still not owe Impax any payment under the SLA.[29]

27. At the time Impax and Endo executed the SLA, Impax expected to enter the market, sell generic Opana ER, and potentially make royalty payments to Endo.

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[23] Levin Deposition Trans. (dated 8/10/2017) 98:21-23 (Hassi Decl. Ex. R).

[24] Levin Deposition Trans. (dated 8/10/2017) 97:16-23 (Hassi Decl. Ex. R); Snowden Deposition Trans. (dated 8/2/2017) 205:6-16 (Hassi Decl. Ex. O); Reasons Deposition (dated 8/11/2017) 19:10-17 (Hassi Decl. Ex. S).

[25] IMPAX-OPANA-CID00007034–57 at 12 (Hassi Decl. Ex. J); *contra* Compl., *In re Impax Labs., Inc.*, Dkt. 9373 (Jan. 19, 2017)) ¶ 58 (Leefer Decl. Ex. A).

[26] IMPAX-OPANA-CID00007034–57 (Hassi Decl. Ex. J); Reasons Deposition (dated 8/11/2017) 25:19-21 (Hassi Decl. Ex. S).

[27] IMPAX-OPANA-CID00007034–57 at 12 (Hassi Decl. Ex. J); Reasons Deposition (dated 8/11/2017) 15:17-19 (Hassi Decl. Ex. S); *see also* Complaint Counsel's Responses to Impax's First Set of Requests for Admission, at 10, 11 (Hassi Decl. Ex. M); *see also* Compl., *In re Impax Labs., Inc.*, Dkt. 9373 (Jan. 19, 2017) ¶ 67 (Leefer Decl. Ex. A), Answer, *In re Impax Labs., Inc.*, Dkt. 9373 (Feb. 7, 2017)) ¶ 67 (Leefer Decl. Ex. B).

[28] IMPAX-OPANA-CID00007034–57 at 12 (Hassi Decl. Ex. J); Reasons Deposition (dated 8/11/2017) 15:17-19 (Hassi Decl. Ex. S); Denied in Complaint Counsel's Responses to Impax's First Set of Requests for Admission, at 10 (Hassi Decl. Ex. M); *see also* Mot. for Summary Decision, *In re Impax Labs., Inc.*, Dkt. 9373 (August 3, 2017), Complaint Counsel's Statement of Undisputed Facts ¶ 24.

[29] IMPAX-OPANA-CID00007034–57 at 12 (Hassi Decl. Ex. J); Reasons Deposition (dated 8/11/2017) 15:17-19 (Hassi Decl. Ex. S); Snowden Deposition Trans. (dated 8/2/2017) 205:17-206:21 (Hassi Decl. Ex. O); Smolenski Deposition (dated 7/18/2017) 194:11-19 (Hassi Decl. Ex. T).

28. The payment Impax received under the Endo Credit terms came years after the execution of the SLA and was due to unforeseen events partially outside of Endo's control and wholly outside of Impax's control.[30]

29. [redacted][1]

30. The Endo Credit and No-AG terms were not mutually exclusive; if Endo did not owe Impax a payment under the Endo Credit term, Impax would not necessarily benefit from the No-AG term of the SLA.

31. Impax did not benefit from the No-AG term.[32]

Development and Co-Promotion Agreement:

32. The Development and Co-Promotion Agreement ("DCA") contained actual and potential payments to Impax that were a fair value exchange for the profit-sharing rights Endo received and the services Impax agreed to provide.[33]

33. The DCA made financial and business sense for both Endo and Impax without taking into consideration the SLA.[34]

34. Endo's $10 million initial payment to Impax under the DCA was to contribute to the substantial anticipated development costs of a specific formulation of IPX203, described

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[30] *See, e.g.*, Impax_Opana_PartIII_0063870 (Hassi Decl. Ex. U).

[31] IMPAX-OPANA-CID00001716–IMPAX-OPANA-CID00001726 (Hassi Decl. Ex. V).

[32] IMS Sales Data, Impax_Opana_PartIII_0000005 (showing no Endo sales of an authorized generic) (Hassi Decl. ¶ 15).

[33] IMPAX-OPANA-CID00011840-72 at § 2.1 (Hassi Decl. Ex. W); *see* Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Requests for Admission, at 11-13 (Hassi Decl. Ex. DD); Complaint Counsel's Objections and Responses to Respondent Impax Laboratories, Inc.'s First Set of Interrogatories to Complaint Counsel, at 5-6 (Hassi Decl. Ex. EE).

[34] Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Third Set of Interrogatories, No. 11 (Hassi Decl. Ex. G); Bradley Deposition (dated 7/6/2017) 155:2-8 (Hassi Decl. Ex. X); Nestor Deposition (dated 8/4/2017) 116:6-23 (Hassi Decl. Ex. Y).

in the DCA, which both parties envisioned would be an improved version of Impax's drug Rytary® and a follow-on product thereto.[35]

35. As part of the DCA, Endo also committed to make additional financial contributions to the development of this IPX203 formulation if Impax achieved certain research and development milestones.[36]

36. Before executing the DCA, Impax expected the development costs associated with IPX203 to be at least $[redacted].[37]

37. In exchange for the actual and potential payments under the DCA, Endo received potentially lucrative profit-sharing rights if the target formulation was successfully commercialized, based on sales resulting from non-neurologist prescriptions in the United States.[38]

38. Impax did extensive R&D work over a period of years on the formulation of IPX203. [redacted][39]

39. [redacted][40]

[35] *See* Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories, at 25-26 (Leefer Decl. Ex. BB)*; contra* Compl., *In re Impax Labs., Inc.*, Dkt. 9373 (Jan. 19, 2017) ¶ 76(b)-(d), (g) (Leefer Decl. Ex. A).

[36] *See* Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories, at 22 (Leefer Decl. Ex. BB).

[37] *See* Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Second Set of Interrogatories, at 25; Nestor Deposition (dated 8/4/2017) 95:5-16 (Hassi Decl. Ex. Y).

[38] IMPAX-OPANA-CID00011840-72 at § 2.1 (Hassi Decl. Ex. W); *see also* Bradley Deposition (dated 7/6/2017) 155:2-8 (Hassi Decl. Ex. X).

[39] Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Third Set of Interrogatories, at 12 (Hassi Decl. Ex. G).

[40] *Id.* at 13.

40. Impax has continued to pursue the new formulation of IPX203, still a strategically important product candidate for the company which could lead to an improved treatment for Parkinson's patients.[41]

41. [redacted], Impax had devoted extensive time and resources to the IPX203 formulation as defined in the DCA, including significant labor hours, clinical studies, and research and development expenses, at a cost to Impax that far exceeds $[redacted] million.[42]

[41] *See* Respondent Impax Labs. Inc.'s Objections and Responses to Compl. Counsel's Requests for Admission, at 11-12 (Hassi Decl. Ex. DD); *see also, e.g.*, Impax_Opana_PartIII_0061614–Impax_Opana_PartIII_0061628 (Hassi Decl. Ex. FF).

[42] *See* CID Narrative Response To Specification No. 26 (July 8, 2014); Impax_Opana_PartIII_0081315 (showing R&D hours expended on IPX203) (Hassi Decl. Ex. Z); *see also* Nestor Deposition (dated 8/4/2017) 95:5-16 (predicting development would cost between $[redacted]) (Hassi Decl. Ex. Y).

Dated: August 31, 2017

By: */s/ Edward D. Hassi*

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Counsel for Impax Laboratories, Inc.

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

COMMISSIONERS: **Maureen K. Ohlhausen, Acting Chairman**
Terrell McSweeny

In the Matter of: IMPAX LABORATORIES, INC., a corporation.	**Docket No. 9373**

DECLARATION OF EDWARD D. HASSI IN SUPPORT OF RESPONDENT IMPAX LABORATORIES, INC.'S OPPOSITION TO COMPLAINT COUNSEL'S MOTION FOR SUMMARY DECISION

I, Edward D. Hassi, hereby state and declare as follows:

1. I am an attorney at O'Melveny & Myers LLP ("O'Melveny"). I am licensed and authorized to practice law in the District of Columbia. I am over the age of 18, am capable of making this Declaration, know all of the following facts of my own personal knowledge, and, if called and sworn as a witness, could and would testify competently thereto. I declare under the penalty of perjury that the foregoing is true and correct.
2. Exhibit A is a true and correct copy of Complaint Counsel's First Set of Interrogatories to Impax Laboratories, Inc.
3. Exhibit B is a true and correct copy of Complaint Counsel's Motion to Compel Response to Interrogatory Nos. 2 & 3.
4. Exhibit C is a true and correct copy of the Second Revised Scheduling Order, issued in the above-captioned matter on June 19, 2017.
5. Exhibit D is a true and correct copy of the Confidential Memorandum of Impax Laboratories, Inc. to the Federal Trade Commission Staff dated February 16, 2015.

6. Exhibit E is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00000017–IMPAX-OPANA-CID00000018.
7. Exhibit F is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00000019–IMPAX-OPANA-CID00000020.
8. Exhibit G is a true and correct copy of Respondent Impax Laboratories, Inc.'s Objections and Responses to Complaint Counsel's Third Set of Interrogatories.
9. Exhibit H is a true and correct copy of an Order on Claim Construction, issued in case No. 09-831 in federal court in the District of New Jersey on Mar. 30, 2010.
10. Exhibit I is a true and correct copy of an excerpt from the Deposition Transcript of Arthur Koch taken on June 6, 2017.
11. Exhibit J is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00007034–IMPAX-OPANA-CID00007057.
12. Exhibit K is a true and correct copy of the Trial Opinion issued in *Endo Pharmaceuticals Inc. v. Actavis*, Inc., No. 14-cv-1381-RGA (D. Del., Aug. 30, 2017).
13. Exhibit L is a true and correct of the Complaint filed in *Endo Pharmaceuticals Inc. v. Par Pharmaceuticals Co.,* No. 13-cv-3284 (S.D.N.Y. May 15, 2013).
14. Exhibit M is a true and correct copy of Complaint Counsel's Responses to Impax's First set of Requests for Admission.
15. Publically available IMS data, cited in the Statement of Facts, is too voluminous to attach as an Exhibit to this Declaration; a copy can be made available to the court upon request.
16. Exhibit N is a true and correct copy of an excerpt from the FDA's Orange Book Website for drugs with the active ingredient oxymorphone, available at https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm.

17. Exhibit O is a true and correct copy of an excerpt from the Deposition Transcript of Meg Snowden taken on August 2, 2017.
18. Exhibit P is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00019449–IMPAX-OPANA-CID00019450.
19. Exhibit Q is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00012004.
20. Exhibit R is a true and correct copy of an excerpt from the Deposition Transcript of Alan Levin taken on August 10, 2017.
21. Exhibit S is a true and correct copy of an excerpt from the Deposition Transcript of Bryan Reasons taken on August 11, 2017.
22. Exhibit T is a true and correct copy of an excerpt from the Deposition Transcript of Ted Smolenski taken on July 18, 2017.
23. Exhibit U is a true and correct copy of a document bearing bates number Impax_Opana_PartIII_0063870.
24. Exhibit V is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00001716–IMPAX-OPANA-CID00001726.
25. Exhibit W is a true and correct copy of a document bearing bates number IMPAX-OPANA-CID00011840–IMPAX-OPANA-CID00011872.
26. Exhibit X is a true and correct copy of an excerpt from the Deposition Transcript of Mark Bradley taken on July 6, 2017.
27. Exhibit Y is a true and correct copy of an excerpt from the Deposition Transcript of Michael Nestor taken on August 4, 2017.

28. Exhibit Z is a true and correct copy of a document bearing bates number Impax_Opana_PartIII_0081315.
29. Exhibit AA is a true and correct copy of a document bearing bates number Impax_Opana_PartIII_0037996.
30. Exhibit BB is a true and correct copy of the Complaint filed in *Endo Pharmaceuticals Inc. v. Actavis Inc.*, No. 12-cv-8985 (S.D.N.Y. Dec. 11, 2012).
31. Exhibit CC is a true and correct copy of *Endo Pharmaceuticals Inc. v. Actavis Inc.*, 746 F.3d 1371 (Fed. Cir. 2014).
32. Exhibit DD is a true and correct copy of Respondent Impax Laboratories, Inc.'s Objections and Responses to Complaint Counsel's Requests for Admission.
33. Exhibit EE is a true and correct copy of Complaint Counsel's Objections and Responses to Respondent Impax Laboratories, Inc.'s First Set of Interrogatories.
34. Exhibit FF is a true and correct copy of a document bearing bates number Impax_Opana_PartIII_0061614–Impax_Opana_PartIII_0061628.
35. Exhibit GG is a true and correct copy of the Complaint filed in *Endo Pharmaceuticals, Inc. v. Impax Laboratories, Inc.*, No. 2:09-cv-0831-KSH-PS (D.N.J. Jan. 25, 2008).

Executed this 31st day of August 2017 in Washington, DC.

By: */s/ Edward D. Hassi*
Edward D. Hassi

EXHIBIT A

1410004

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of **Impax Laboratories, Inc.,** **a corporation.**	**Docket No. 9373**

COMPLAINT COUNSEL'S FIRST SET OF INTERROGATORIES TO IMPAX LABORATORIES, INC.

Pursuant to the Federal Trade Commission's Rules of Practice, 16 C.F.R. §§ 3.31 and 3.35, Complaint Counsel hereby requests that the Respondent answer the following Interrogatories within 30 days from the date of service thereof or in such lesser time as the Administrative Law Judge may allow pursuant to Rule of Practice 3.35(a)(2):

1. Identify any joint defense or common interest between You and Endo in any actual or potential litigation (including, but not limited to, *FTC v. Endo Pharmaceuticals Inc.*, Case No. 16-cv-01440 (E.D. Pa. filed March 30, 2016), *Endo Pharmaceuticals Inc. v. FTC*, Case No. 16-cv-05600 (E.D. Pa. filed Oct. 16, 2016), and *In re Opana Antitrust Litigation*, Case Nos. 1:14-cv-10150, 1:14-cv-07320, and 15-cv-00269 (N.D. Ill.)), and describe the subject matter and scope of any joint defense or common interest.

2. Identify all procompetitive justifications and benefits to consumers and the public interest referenced in the Eighth Defense in Your Answer to the Complaint in this case, and explain the factual basis for Your answer to this Interrogatory, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

3. For each procompetitive justification and benefit identified in response to Interrogatory No. 2, explain how the No-AG Provision and the Endo Credit provision contained in the Opana ER Settlement and License Agreement were reasonably necessary to achieve that benefit, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

DEFINITIONS

1. The terms "Impax," "Company," "You," or "Your" mean Impax Laboratories, Inc., its directors, officers, trustees, employees, attorneys, agents, accountants, consultants, and representatives, its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, partnerships and joint ventures, and the directors, officers, trustees, employees, attorneys, agents, consultants, and representatives of its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, and partnerships and joint ventures.

2. The terms "and" and "or" have both conjunctive and disjunctive meanings.

3. The term "Communication" means any transmittal, exchange, transfer, or dissemination of information, regardless of the means by which it is accomplished, and includes all communications, whether written or oral, and all discussions, meetings, telephone communications, or email contacts.

4. The term "Complaint" means the Complaint issued in this matter, *In re Impax Laboratories, Inc.*, FTC Docket No. 9373.

5. The term "Documents" means all written, recorded, transcribed, or graphic matter of every type and description, however and by whomever prepared, produced, reproduced, disseminated, or made, including, but not limited to, analyses, letters, telegrams, memoranda, reports, bills, receipts, telexes, contracts, invoices, books, accounts, statements, studies, surveys, pamphlets, notes, charts, maps, plats, tabulations, graphs, tapes, data sheets, data processing cards, printouts, net sites, microfilm, indices, calendar or diary entries, manuals, guides, outlines, abstracts, histories, agendas, minutes or records of meetings, conferences, electronic mail, and telephone or other conversations or Communications, as well as films, tapes, or slides, and all other data compilations in the possession, custody, or control of the Company, or to which the Company has access. The term "documents" includes the complete original document (or a copy thereof if the original is not available), all drafts (whether or not they resulted in a final document), and all copies that differ in any respect from the original, including any notation, underlining, marking, or information not on the original.

6. The term "each," "any," and "all" mean "each and every."

7. The term "Endo" means Endo International plc, its directors, officers, trustees, employees, attorneys, agents, accountants, consultants, and representatives, its domestic and foreign parents, predecessors, divisions, subsidiaries (including, but not limited to, Endo Pharmaceuticals Inc.), affiliates, partnerships and joint ventures, and the directors, officers, trustees, employees, attorneys, agents, consultants, and representatives of its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, and partnerships and joint ventures.

8. The term "Endo Credit" means Section 4.4 of the Opana ER Settlement and License Agreement.

9. The term "Identify" means to state:

a) in the case of a natural person, his or her name, employer, business address and telephone number, title or position, and dates the person held that position(s);

b) in the case of a Person other than a natural person, its name and principal address, telephone number, and name of a contact person;

c) in the case of a document, the title of the document, the author, the title or position of the author, the addressee, each recipient, the type of document, the subject matter, the date of preparation, and its number of pages; and

d) in the case of a communication, the date of the communication, the parties to the communication, the method of communication (oral, written, etc.), and a description of the substance of the information exchanged during the communication.

10. The term "No-AG Provision" means Section 4.1(c) of the Opana ER Settlement and License Agreement.

11. The term "Opana ER Settlement and License Agreement" means the Settlement and License Agreement between Endo, Penwest, and Impax signed on June 7, 2010, and effective on June 8, 2010.

12. The term "Person" includes the Company, and means any natural person, corporate entity, partnership, association, joint venture, governmental entity, trust, or any other organization or entity engaged in commerce.

INSTRUCTIONS

1. The relevant period for each Interrogatory is January 1, 2008 to the present.

2. Provide separate and complete sworn responses for each Interrogatory and subpart. Please note that under 16 C.F.R. §3.35, interrogatories directed to a corporation shall be answered by an "officer or agent," "[e]ach interrogatory shall be answered separately and fully in writing under oath," and "[t]he answers are to be signed by the person making them, and the objections signed by the attorney making them." *See* 16 C.F.R. §§3.35(a), (b), (c).

3. State if You are unable to answer any of the Interrogatories herein fully and completely after exercising due diligence to secure the information necessary to make full and complete answers. Specify the reason(s) for Your inability to answer any portion or aspect of such Interrogatory, including a description of all efforts You made to obtain the information necessary to answer the Interrogatory fully.

4. Answer each Interrogatory fully and completely based on the information and knowledge currently available to You, regardless of whether You intend to supplement Your response upon the completion of discovery. *See North Texas Specialty Physicians*, FTC Docket No. 9312 (April 11, 2002) (Complaint Counsel must provide "full and complete responses . . . with the information and facts it currently has available") (Chappell, A.L.J.).

5. If You object or otherwise decline to set forth in Your response any of the information requested by any Interrogatory, set forth the precise grounds upon which You rely with specificity so as to permit the Administrative Law Judge or other administrative or judicial entity to determine the legal sufficiency of Your objection or position, and provide the most responsive information You are willing to provide without an order.

6. Your answers to any Interrogatory herein must include all information within Your possession, custody or control, including information reasonably available to You and Your agents, attorneys or representatives.

7. If in answering any of the Interrogatories You claim any ambiguity in either the Interrogatory or any applicable definition or instruction, identify in Your response the language You consider ambiguous and state the interpretation You are using in responding.

8. Each Interrogatory herein is continuing and requires prompt amendment of any prior response if You learn, after acquiring additional information or otherwise, that the response is in some material respect incomplete or incorrect. See 16 C.F .R. § 3.31(e).

9. If You object to any Interrogatory or any portion of any Interrogatory on the ground that it requests information that is privileged (including the attorney-client privilege) or falls within the attorney work product doctrine, state the nature of the privilege or doctrine You claim and provide all other information as required by 16 C.F.R. § 3.38A.

10. The singular form of a word shall be interpreted as plural, and the plural form of a word shall be interpreted as singular, so as to bring within the scope of the Interrogatory that which might otherwise be excluded.

11. "And" and "or" are to be interpreted inclusively so as not to exclude any information otherwise within the scope of any request.

12. None of the Definitions or Interrogatories set forth herein shall be construed as an admission relating to the existence of any evidence, to the relevance or admissibility of any evidence, or to the truth or accuracy of any statement or characterization in the Definition or Interrogatory.

13. Whenever a verb is used in one tense it shall also be taken to include all other tenses, so as to bring within the scope of the Interrogatory that which might otherwise be excluded.

14. All words that are quoted from the Complaint filed in this matter have the same meaning as those used therein.

15. For each natural person You refer to in Your answers, state (1) that person's full name; (2) the person's last known business address and business phone number, or where that person's business address and phone number is unavailable, that person's home address and home phone number; (3) the person's business affiliation and title during the time period of the matter at issue; and (4) the person's current business affiliation and title.

Dated: April 5, 2017

By: _*/s/ Bradley S. Albert*_____

Bradley S. Albert
FEDERAL TRADE COMMISSION
Bureau of Competition
400 7th Street, SW
Washington, DC 20024
balbert@ftc.gov
Telephone: (202) 326-3670

Counsel Supporting the Complaint

CERTIFICATE OF SERVICE

I hereby certify that on April 5, 2017, I served via electronic mail a true copy of the foregoing document on:

Edward D. Hassi
O'MELVENY & MYERS LLP
1625 Eye Street, NW
Washington, D.C. 20006
ehassi@omm.com

Counsel for Respondent Impax

By: */s/ Rebecca E. Weinstein*
Rebecca E. Weinstein

Counsel Supporting the Complaint
Bureau of Competition
Federal Trade Commission
Washington, D.C. 20024

EXHIBIT B

PUBLIC

ORIGINAL

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	**DOCKET NO. 9373**
Respondent	)	

COMPLAINT COUNSEL'S
MOTION TO COMPEL RESPONSE TO INTERROGATORY NOS. 2 & 3

Bradley S. Albert
Deputy Assistant Director

Charles A. Loughlin
Chief Trial Counsel

Daniel W. Butrymowicz
Alpa D. Davis
Nicholas A. Leefer
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Dated: June 1, 2017

COMPLAINT COUNSEL'S MOTION TO COMPEL RESPONSE TO INTERROGATORY NOS. 2 & 3

TO ALL PARTIES AND THEIR COUNSEL OF RECORD:

Please take notice that, pursuant to Federal Trade Commission Rule of Practice 3.38(a), Complaint Counsel hereby respectfully requests an order compelling Respondent to provide substantive responses to Complaint Counsel's Interrogatory Nos. 2 & 3. For the reasons set forth in the accompanying Memorandum, this motion should be granted.

This Motion is supported by the accompanying Memorandum and the authorities cited therein. A Proposed Order is attached.

Respectfully submitted,

/s/ Nicholas A. Leefer

Nicholas A. Leefer
Bradley S. Albert
Charles A. Loughlin
Daniel W. Butrymowicz
Alpa D. Davis
Synda Mark
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Counsel Supporting the Complaint

Dated: June 1, 2017

PUBLIC

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	**DOCKET NO. 9373**
Respondent	)	

MEMORANDUM OF LAW IN SUPPORT OF COMPLAINT COUNSEL'S MOTION TO COMPEL RESPONSE TO INTERROGATORY NOS. 2 & 3

Bradley S. Albert
Deputy Assistant Director

Charles A. Loughlin
Chief Trial Counsel

Daniel W. Butrymowicz
Alpa D. Davis
Nicholas A. Leefer
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Lauren Peay
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Dated: June 1, 2017

PUBLIC

This case challenges an anticompetitive reverse-payment agreement between Impax and Endo to obstruct lower-cost generic competition to Opana ER, a pain-relief medication. Under this agreement, Impax accepted large payments in cash and other valuable consideration in exchange for its commitment not to compete for 2 ½ years. In *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013), the Supreme Court held that such "reverse payments" can violate the antitrust laws and should be evaluated under the rule of reason applicable to most antitrust cases. Under the well-established burden-shifting framework used in antitrust rule-of-reason cases, Impax has the burden of establishing a legitimate justification for the reverse payment it received.

In its Answer, Impax asserts that the alleged conduct had "substantial pro-competitive justifications," but does not identify or provide any other information about these purported procompetitive justifications. Answer at 21. To obtain the information necessary to conduct meaningful discovery, Complaint Counsel propounded two interrogatories, asking Impax to identify (1) the purported procompetitive justifications, and (2) how the reverse payments were reasonably necessary to achieve those benefits. Impax refused to answer these interrogatories on the ground that they are "contention interrogatories, to which Impax need not respond until the close of discovery, if at all." Declaration of Nicholas A. Leefer ("Leefer Decl.") Exhibit C at 2.

Complaint counsel respectfully submits that Impax should answer these interrogatories now. They seek discovery at the heart of this case: whether Impax can demonstrate legitimate, cognizable, procompetitive justifications for the reverse payment. Both interrogatories clearly can be answered at this time; Impax has no need to take its own discovery to identify whatever justifications it claims exist. By refusing to answer these interrogatories until the "close of discovery, if at all," Impax is denying Complaint Counsel the opportunity to conduct meaningful

discovery into the bases for Impax's affirmative defense. Accordingly, the Court should order Impax to provide a substantive response to Interrogatory Nos. 2 & 3.

I. FACTUAL BACKGROUND

On February 07, 2017, Impax filed its Answer to the Complaint. In the Answer, Impax asserted ten affirmative defenses, including its eighth defense:

> The alleged conduct had substantial pro-competitive justifications, benefited consumers and the public interest, and avoided potential infringement of valid patents. These pro-competitive justifications outweigh any alleged anticompetitive effects of the alleged conduct. There were no less restrictive alternatives that could have achieved these same pro-competitive outcomes.

Answer at 21. Although Impax will bear the burden of proof in advancing its purported procompetitive justifications and consumer benefits, it has pleaded no facts to support its eighth asserted defense.

To understand the scope of Impax's asserted defense, Complaint Counsel served its first set of interrogatories on April 5, 2017. *See* Leefer Decl. Exhibit A. Interrogatory Nos. 2 & 3 sought information related to Impax's eighth defense:

> **Interrogatory No. 2**
> Identify all procompetitive justifications and benefits to consumers and the public interest referenced in the Eighth Defense in Your Answer to the Complaint in this case, and explain the factual basis for Your answer to this Interrogatory, including identifying all facts and documents You rely on in Your answer to this Interrogatory.
>
> **Interrogatory No. 3**
> For each procompetitive justification and benefit identified in response to Interrogatory No. 2, explain how the No-AG Provision and the Endo Credit provision contained in the Opana ER Settlement and License Agreement were reasonably necessary to achieve that benefit, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

On May 5, 2017, Impax served its objections and responses. Rather than respond substantively, it merely objected that these were contention interrogatories, and refused to

respond until the close of discovery. *See* Leefer Decl. Exhibit B. To resolve this discovery dispute Complaint Counsel proposed a compromise: Impax could wait until the close of discovery to identify the factual bases for its asserted procompetitive justifications and benefits, but that it would identify now the claimed procompetitive justifications and benefits and explain why the provisions of the settlement agreement were necessary to achieve those benefits. *See* Leefer Decl. Exhibit C at 3. Impax rejected this compromise, and instead recycled a three-year-old response to a much narrower CID Specification from the FTC's investigation. *Id*. at 1-2.

II. ARGUMENT

A. Interrogatory Nos. 2 & 3 seek relevant information

"Parties may obtain discovery to the extent that it may be reasonably expected to yield information relevant to the allegations of the complaint, to the proposed relief, or to the defenses of any respondent." 16 C.F.R. § 3.31(c)(1). In its Answer, Impax has raised purported procompetitive justifications as an affirmative defense. The interrogatories at issue seek a description of and other information relating to that affirmative defense. Thus, notwithstanding Impax's boilerplate objections, the interrogatories unquestionably seek relevant information. *See Liguria Foods, Inc. v. Griffith Labs., Inc.*, No. C14-3041, 2017 U.S. Dist. LEXIS 35370, at *51 (N.D. Iowa Mar. 13, 2017) ("Federal discovery rules and the cases interpreting them uniformly finding the 'boilerplate' discovery culture impermissible are not aspirational, they are the law.").

B. Interrogatory Nos. 2 & 3 should be answered now to allow Complaint Counsel to conduct meaningful discovery of Impax's affirmative defenses

An answer to these interrogatories at this time is both appropriate and necessary to allow Complaint Counsel to conduct discovery and prepare for trial. To be sure, the FTC's Rules of Practice presume that a party may wait to answer contention interrogatories until the end of discovery. But, the rules also contemplate that in appropriate circumstances contention

interrogatories should be answered at an earlier stage. *See* Rules of Practice; Final Rule, 74 Fed. Reg. 1804, 1815 (Jan. 13, 2009) (amending 16 C.F.R. pt. 3 and 4) ("[T]he proposed Rule also allowed a party posing a contention interrogatory to secure an earlier answer, if one was necessary, by filing a motion seeking an earlier answer."); *see also* Rules of Practice; Proposed Rule, 73 Fed. Reg. 58832, 58839 (Oct. 7, 2008) (amending 16 C.F.R. pt. 3 and 4) ("If a party poses a contention interrogatory that is capable of being answered at an earlier time, there is no reason it could not move to compel a more expeditious response."). This is one of those circumstances.

Basic fairness dictates that a party raising a claim or defense disclose such claim or defense and the factual basis for it. *See* 16 C.F.R. § 3.31(b)(2) (requiring initial disclosures that include "a copy of, or a description by category and location of, all documents and electronically stored information…that are relevant to…the defenses of the respondent…"). A party "is not excused from making its disclosures because it has not fully completed its investigation." *Id*. This makes sense; absent early disclosure of affirmative defenses and related facts, Complaint Counsel has no opportunity to question witnesses, request documents, or seek admissions related to those affirmative defenses. Impax's refusal to specify its purported procompetitive justifications and benefits impairs Complaint Counsel' ability to prepare for trial.

This logic applies equally regardless of whether Interrogatory Nos. 2 & 3 are labeled "contention interrogatories." As the district court observed in *United States v. Blue Cross Blue Shield of Mich.*, No. CV 10-14155, 2012 WL 12930840, at *5 (E.D. Mich. May 30, 2012), an interrogatory seeking "the basis of one of BCBS's defenses—that BCBS's MFN clauses caused procompetitive effects" was "not one that is best served at the end of discovery." This Court reached a similar conclusion in *In re POM Wonderful LLC*, explaining that undue delay in

answering contention interrogatories risks prejudice to the propounding party. Dkt. No. 9344, 2011 FTC LEXIS 42, at *9 (F.T.C. Mar. 16, 2011) ("Undue delay in disclosure of a contention, with the conditions proposed by Complaint Counsel, could hamper Respondents' ability to defend against the charge at trial and thereby present an unnecessary risk of prejudice to Respondents."). As in *POM Wonderful*, Impax's refusal to answer these interrogatories until the "close of discovery, if at all" will hamper Complaint Counsel's ability to prepare for trial, and presents an unnecessary risk of prejudice. For example, once discovery is closed, Complaint Counsel will have no way to test Impax's purported procompetitive justifications through depositions or requests for production.

Requiring Impax to respond to these interrogatories now also has the potential to narrow the issues for discovery and trial. Currently, Complaint Counsel faces the impossible choice of either forgoing discovery into Impax's eighth affirmative defense, or seeking discovery on every conceivable procompetitive justification, without knowing whether Impax may choose to rely on it at trial. The purpose of interrogatories in discovery is to avoid this outcome. *See In re TK-7 Corp.*, Dkt. No. 9224, 1990 FTC LEXIS 20, at *1-2 (F.T.C. Mar. 9, 1990) ("The purpose of interrogatories is to narrow the issues and thus help determine what evidence will be needed at the trial and to reduce the possibility of surprise at the trial.").

Notwithstanding these good reasons for answering the interrogatories now, Impax provides no reason why it is unable to do so. To plead procompetitive justifications in the Answer, Impax must already have a good faith basis in fact and law. *See Dot Com Entm't Grp., Inc. v. Cyberbingo Corp.*, 237 F.R.D. 43, 45-6 (W.D.N.Y. 2006) ("Defendants are expected to have, even at an early stage, some good faith basis in fact and law for such claim and defense…Accordingly, Plaintiff's Interrogatories which primarily seek the basis for the defense

and related counterclaim, even if they are assumed to constitute contention interrogatories, should be answered at this time."). *See also* 16 C.F.R. § 4.2(f)(2) ("Signing a document constitutes a representation by the signer that…to the best of his or her knowledge, information, and belief, the statements made in it are true…"). Thus, even though it failed to include any detail in its Answer, Impax must already know what it claims are the asserted procompetitive justifications and benefits and how the payment provisions of the settlement agreement were reasonably necessary to achieve such benefits. Impax has no need to conduct discovery on this issue. Such information will be found—if it exists at all—in the knowledge of Impax's witnesses and its own documents.

Moreover, requiring an answer to these interrogatories now does not prejudice Impax. To the extent that Impax intends to develop additional information throughout discovery, Impax may supplement its responses; that is not a reason to refuse to respond at all until after discovery closes. *See In re N. Tex. Specialty Physicians*, Dkt. No. 9312, 2003 FTC LEXIS 180, at *5 (F.T.C. Dec. 4, 2003) (ordering answers to contention interrogatories and citing 16 C.F.R. § 3.31(e) for the proposition that the party must supplement its answers to the extent it obtains additional information later).

C. At a minimum, Impax should be required to identify its purported procompetitive justifications and benefits, and explain how the reverse payments were reasonably necessary to achieve those benefits

Even if the Court concludes that Impax need not answer the contention portion of the interrogatories until the close of discovery, the Court should require Impax to answer Interrogatory Nos. 2 & 3 as narrowed by Complaint Counsel's proposed compromise. Under this proposed compromise, Interrogatory No. 2 merely asks for the identification of Impax's purported procompetitive justifications and benefits, and Interrogatory No. 3 seeks an

explanation of how the provisions of the settlement agreement relate to Impax's purported procompetitive justifications. *See* Leefer Decl. Exhibit C at 3. As narrowed, Complaint Counsel is simply seeking the particularization of Impax's asserted affirmative defenses.

Interrogatories that ask a party to particularize its defenses are not contention interrogatories—that is, interrogatories that "involve[] an opinion or contention that relates to fact or the application of law to fact." 16 C.F.R. § 3.35(b)(2). *See Dot Com Entm't Grp., Inc.*, 237 F.R.D. at 44 (holding that an interrogatory demanding that "Defendants particularize, *i.e.*, 'identify,' the prior art upon which Defendants' prior art defense is predicated" was not a contention interrogatory); *see also Intelligent Verification Systems, LLC v. Microsoft Corp.*, No. 2:12-cv-525, 2015 WL 846012, at *4 (E.D. Va. Feb. 25, 2015) ("Strikingly absent from Interrogatory No. 6 is any request for an opinion or contention as contemplated by Rule 33(c).") (*internal quotation omitted*). As in *Dot Com Entm't Grp*, Interrogatory No. 2 does not ask Impax "to explain why or how, as a matter of opinion or otherwise," its purported justifications are procompetitive, or require Impax to "advance legal argument in support of [its] defense..." *Dot Com Entm't Grp., Inc.*, 237 F.R.D. at 44. And, although Interrogatory No. 3 does ask Impax to explain "how" the reverse payments from the settlement agreement were necessary to achieving the purported procompetitive effects, this is a factual inquiry into why the payments were included in the settlement, not a request for opinion or legal argument. As narrowed, both interrogatories are easily answered based on Impax's current knowledge, and should be answered so that Complaint Counsel has a meaningful opportunity to conduct appropriate discovery.

CONCLUSION

For the reasons stated above, Complaint Counsel's Motion to Compel should be granted.

Respectfully submitted,

/s/ Nicholas A. Leefer

Nicholas A. Leefer
Bradley S. Albert
Charles A. Loughlin
Daniel W. Butrymowicz
Alpa D. Davis
Synda Mark
Lauren Peay
Maren J. Schmidt
Eric M. Sprague
Jamie Towey
James H. Weingarten

Counsel Supporting the Complaint

Dated: June 1, 2017

PUBLIC

STATEMENT REGARDING MEET AND CONFER

The undersigned counsel certifies that Complaint Counsel conferred with Respondent's counsel in a good faith effort to resolve by agreement the issues raised by Respondent's Objections and Responses to Complaint Counsel's First Set of Interrogatories. On May 9, 2017, Complaint Counsel (Nicholas Leefer) responded to Impax's objections with a proposed compromise, and asked to meet and confer. On May 16, 2017, Complaint Counsel (Nicholas Leefer, Bradley Albert, and Maren Schmidt) and Respondent's Counsel (Anna Fabish) communicated by telephone. And on May 22, 2017, Complaint Counsel (Nicholas Leefer) and Respondent's Counsel (Anna Fabish) communicated by email.

Dated: June 1, 2017

Respectfully submitted,

/s/ Nicholas A. Leefer

Nicholas A. Leefer
Federal Trade Commission
600 Pennsylvania Ave, NW
Washington, DC 20580

PUBLIC

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	**DOCKET NO. 9373**
Respondent	)	

[PROPOSED] ORDER

Having carefully considered Complaint Counsel's Motion to Compel Response to Interrogatory Nos. 2 & 3, Respondent's Opposition thereto, all supporting evidence, and the applicable law, it is hereby ORDERED that Complaint Counsel's Motion to Compel Response to Interrogatory Nos. 2 & 3 is GRANTED and it is hereby ORDERED that, no later than June 15, 2017, Respondent shall provide full and complete answers to Interrogatory Nos. 2 & 3 from Complaint Counsel's First Set of Interrogatories.

ORDERED:

_____
D. Michael Chappell
Chief Administrative Law Judge

Date: _____

CERTIFICATE OF SERVICE

I hereby certify that on June 1, 2017, I filed the foregoing documents electronically using the FTC's E-Filing System, which will send notification of such filing to:

Donald S. Clark
Secretary
Federal Trade Commission
600 Pennsylvania Ave., NW, Rm. H-113
Washington, DC 20580

The Honorable D. Michael Chappell
Administrative Law Judge
Federal Trade Commission
600 Pennsylvania Ave., NW, Rm. H-110
Washington, DC 20580

I also certify that I delivered via electronic mail a copy of the foregoing documents to:

Edward D. Hassi
Michael E. Antalics
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Counsel for Respondent Impax Laboratories, Inc.

Dated: June 1, 2017

By: /s/ Nicholas A. Leefer
Attorney

CERTIFICATE FOR ELECTRONIC FILING

I certify that the electronic copy sent to the Secretary of the Commission is a true and correct copy of the paper original and that I possess a paper original of the signed document that is available for review by the parties and the adjudicator.

June 1, 2017 By: /s/ Nicholas A. Leefer
Attorney

PUBLIC

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	**DOCKET NO. 9373**
Respondent	)	

DECLARATION OF NICHOLAS A. LEEFER

1. I am an attorney at the Federal Trade Commission and Complaint Counsel in this proceeding. Attached to this declaration are the exhibits submitted in support of Complaint Counsel's Memorandum in Support of its Motion to Compel Response to Interrogatory Nos. 2 & 3
2. I have personal knowledge of the facts set forth in this declaration, and if called as a witness I could and would testify competently under oath to such facts.
3. Exhibit A is a true and correct copy of Complaint Counsel's First Set of Interrogatories to Impax Laboratories, Inc.
4. Exhibit B is a true and correct copy of Respondent Imax Laboratories' Objections and Responses to Complaint Counsel's First Set of Interrogatories.
5. Exhibit C is a true and correct copy of an email exchange consisting of an email from Anna Fabish to Nicholas Leefer and others, dated May 5, 2017, an email from Nicholas Leefer to Anna Fabish and others, dated May 9, 2017, an email from Anna Fabish to Nicholas Leefer and others, dated May 22, 2017, an email from Nicholas Leefer to Anna

Fabish and others, dated May 22 2017, and an email from Anna Fabish to Nicholas Leefer and others, dated May 24, 2017.

I declare under the penalty of perjury that the foregoing is true and correct. Executed this 1st day of June, 2017 in Washington, DC.

/s/ Nicholas A. Leefer

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Email: nleefer@ftc.gov

Counsel Supporting the Complaint

PUBLIC

Exhibit A

1410004

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of **Impax Laboratories, Inc.,** **a corporation.**	**Docket No. 9373**

COMPLAINT COUNSEL'S FIRST SET OF INTERROGATORIES TO IMPAX LABORATORIES, INC.

Pursuant to the Federal Trade Commission's Rules of Practice, 16 C.F.R. §§ 3.31 and 3.35, Complaint Counsel hereby requests that the Respondent answer the following Interrogatories within 30 days from the date of service thereof or in such lesser time as the Administrative Law Judge may allow pursuant to Rule of Practice 3.35(a)(2):

1. Identify any joint defense or common interest between You and Endo in any actual or potential litigation (including, but not limited to, *FTC v. Endo Pharmaceuticals Inc.*, Case No. 16-cv-01440 (E.D. Pa. filed March 30, 2016), *Endo Pharmaceuticals Inc. v. FTC*, Case No. 16-cv-05600 (E.D. Pa. filed Oct. 16, 2016), and *In re Opana Antitrust Litigation*, Case Nos. 1:14-cv-10150, 1:14-cv-07320, and 15-cv-00269 (N.D. Ill.)), and describe the subject matter and scope of any joint defense or common interest.

2. Identify all procompetitive justifications and benefits to consumers and the public interest referenced in the Eighth Defense in Your Answer to the Complaint in this case, and explain the factual basis for Your answer to this Interrogatory, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

3. For each procompetitive justification and benefit identified in response to Interrogatory No. 2, explain how the No-AG Provision and the Endo Credit provision contained in the Opana ER Settlement and License Agreement were reasonably necessary to achieve that benefit, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

DEFINITIONS

1. The terms "Impax," "Company," "You," or "Your" mean Impax Laboratories, Inc., its directors, officers, trustees, employees, attorneys, agents, accountants, consultants, and representatives, its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, partnerships and joint ventures, and the directors, officers, trustees, employees, attorneys, agents, consultants, and representatives of its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, and partnerships and joint ventures.

2. The terms "and" and "or" have both conjunctive and disjunctive meanings.

3. The term "Communication" means any transmittal, exchange, transfer, or dissemination of information, regardless of the means by which it is accomplished, and includes all communications, whether written or oral, and all discussions, meetings, telephone communications, or email contacts.

4. The term "Complaint" means the Complaint issued in this matter, *In re Impax Laboratories, Inc.*, FTC Docket No. 9373.

5. The term "Documents" means all written, recorded, transcribed, or graphic matter of every type and description, however and by whomever prepared, produced, reproduced, disseminated, or made, including, but not limited to, analyses, letters, telegrams, memoranda, reports, bills, receipts, telexes, contracts, invoices, books, accounts, statements, studies, surveys, pamphlets, notes, charts, maps, plats, tabulations, graphs, tapes, data sheets, data processing cards, printouts, net sites, microfilm, indices, calendar or diary entries, manuals, guides, outlines, abstracts, histories, agendas, minutes or records of meetings, conferences, electronic mail, and telephone or other conversations or Communications, as well as films, tapes, or slides, and all other data compilations in the possession, custody, or control of the Company, or to which the Company has access. The term "documents" includes the complete original document (or a copy thereof if the original is not available), all drafts (whether or not they resulted in a final document), and all copies that differ in any respect from the original, including any notation, underlining, marking, or information not on the original.

6. The term "each," "any," and "all" mean "each and every."

7. The term "Endo" means Endo International plc, its directors, officers, trustees, employees, attorneys, agents, accountants, consultants, and representatives, its domestic and foreign parents, predecessors, divisions, subsidiaries (including, but not limited to, Endo Pharmaceuticals Inc.), affiliates, partnerships and joint ventures, and the directors, officers, trustees, employees, attorneys, agents, consultants, and representatives of its domestic and foreign parents, predecessors, divisions, subsidiaries, affiliates, and partnerships and joint ventures.

8. The term "Endo Credit" means Section 4.4 of the Opana ER Settlement and License Agreement.

9. The term "Identify" means to state:

a) in the case of a natural person, his or her name, employer, business address and telephone number, title or position, and dates the person held that position(s);

b) in the case of a Person other than a natural person, its name and principal address, telephone number, and name of a contact person;

c) in the case of a document, the title of the document, the author, the title or position of the author, the addressee, each recipient, the type of document, the subject matter, the date of preparation, and its number of pages; and

d) in the case of a communication, the date of the communication, the parties to the communication, the method of communication (oral, written, etc.), and a description of the substance of the information exchanged during the communication.

10. The term "No-AG Provision" means Section 4.1(c) of the Opana ER Settlement and License Agreement.

11. The term "Opana ER Settlement and License Agreement" means the Settlement and License Agreement between Endo, Penwest, and Impax signed on June 7, 2010, and effective on June 8, 2010.

12. The term "Person" includes the Company, and means any natural person, corporate entity, partnership, association, joint venture, governmental entity, trust, or any other organization or entity engaged in commerce.

INSTRUCTIONS

1. The relevant period for each Interrogatory is January 1, 2008 to the present.

2. Provide separate and complete sworn responses for each Interrogatory and subpart. Please note that under 16 C.F.R. §3.35, interrogatories directed to a corporation shall be answered by an "officer or agent," "[e]ach interrogatory shall be answered separately and fully in writing under oath," and "[t]he answers are to be signed by the person making them, and the objections signed by the attorney making them." *See* 16 C.F.R. §§3.35(a), (b), (c).

3. State if You are unable to answer any of the Interrogatories herein fully and completely after exercising due diligence to secure the information necessary to make full and complete answers. Specify the reason(s) for Your inability to answer any portion or aspect of such Interrogatory, including a description of all efforts You made to obtain the information necessary to answer the Interrogatory fully.

4. Answer each Interrogatory fully and completely based on the information and knowledge currently available to You, regardless of whether You intend to supplement Your response upon the completion of discovery. *See North Texas Specialty Physicians*, FTC Docket No. 9312 (April 11, 2002) (Complaint Counsel must provide "full and complete responses . . . with the information and facts it currently has available") (Chappell, A.L.J.).

5. If You object or otherwise decline to set forth in Your response any of the information requested by any Interrogatory, set forth the precise grounds upon which You rely with specificity so as to permit the Administrative Law Judge or other administrative or judicial entity to determine the legal sufficiency of Your objection or position, and provide the most responsive information You are willing to provide without an order.

6. Your answers to any Interrogatory herein must include all information within Your possession, custody or control, including information reasonably available to You and Your agents, attorneys or representatives.

7. If in answering any of the Interrogatories You claim any ambiguity in either the Interrogatory or any applicable definition or instruction, identify in Your response the language You consider ambiguous and state the interpretation You are using in responding.

8. Each Interrogatory herein is continuing and requires prompt amendment of any prior response if You learn, after acquiring additional information or otherwise, that the response is in some material respect incomplete or incorrect. See 16 C.F .R. § 3.31(e).

9. If You object to any Interrogatory or any portion of any Interrogatory on the ground that it requests information that is privileged (including the attorney-client privilege) or falls within the attorney work product doctrine, state the nature of the privilege or doctrine You claim and provide all other information as required by 16 C.F.R. § 3.38A.

10. The singular form of a word shall be interpreted as plural, and the plural form of a word shall be interpreted as singular, so as to bring within the scope of the Interrogatory that which might otherwise be excluded.

11. "And" and "or" are to be interpreted inclusively so as not to exclude any information otherwise within the scope of any request.

12. None of the Definitions or Interrogatories set forth herein shall be construed as an admission relating to the existence of any evidence, to the relevance or admissibility of any evidence, or to the truth or accuracy of any statement or characterization in the Definition or Interrogatory.

13. Whenever a verb is used in one tense it shall also be taken to include all other tenses, so as to bring within the scope of the Interrogatory that which might otherwise be excluded.

14. All words that are quoted from the Complaint filed in this matter have the same meaning as those used therein.

15. For each natural person You refer to in Your answers, state (1) that person's full name; (2) the person's last known business address and business phone number, or where that person's business address and phone number is unavailable, that person's home address and home phone number; (3) the person's business affiliation and title during the time period of the matter at issue; and (4) the person's current business affiliation and title.

Dated: April 5, 2017

By: */s/ Bradley S. Albert*

Bradley S. Albert
FEDERAL TRADE COMMISSION
Bureau of Competition
400 7th Street, SW
Washington, DC 20024
balbert@ftc.gov
Telephone: (202) 326-3670

Counsel Supporting the Complaint

CERTIFICATE OF SERVICE

I hereby certify that on April 5, 2017, I served via electronic mail a true copy of the foregoing document on:

Edward D. Hassi
O'MELVENY & MYERS LLP
1625 Eye Street, NW
Washington, D.C. 20006
ehassi@omm.com

Counsel for Respondent Impax

By: */s/ Rebecca E. Weinstein*
Rebecca E. Weinstein

Counsel Supporting the Complaint
Bureau of Competition
Federal Trade Commission
Washington, D.C. 20024

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Exhibit B

UNITED STATES OF AMERICA
BEFORE THE FEDERAL TRADE COMMISSION

In the Matter of Impax Laboratories, Inc. a corporation	**Docket No. 9373**

RESPONDENT IMPAX LABORATORIES' OBJECTIONS AND RESPONSES TO COMPLAINT COUNSEL'S FIRST SET OF INTERROGATORIES

Respondent Impax Laboratories, Inc. ("Impax") hereby provides the following responses to Complaint Counsel's first set of Interrogatories.

I. PRELIMINARY STATEMENT

The following objections and responses to the FTC's Interrogatories are made on the basis of information that is presently known and available to Impax and may include information that is inadmissible at trial. Respondent's discovery, investigation, and preparation for trial are not yet completed and are continuing as of the date of these objections and responses. Because discovery is ongoing, Respondent expressly reserves the right to continue its discovery and investigation for facts, documents, witnesses, and supplemental data that may reveal information that, if presently within Respondent's knowledge, would have been included in these objections and responses. Respondent's objections and responses are based upon a reasonable investigation and its good-faith understanding of the Interrogatories. Respondent reserves the right to alter or amend its objections and responses if Complaint Counsel's understanding of the Interrogatories differs. Respondent also specifically reserves the right to present additional information at trial, as may be disclosed through continuing investigation and discovery, and specifically reserves the

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right to supplement or modify these objections and responses at any time in light of subsequently discovered information.

The following objections and responses are made without waiving but, instead, preserving: (a) the right to raise in any subsequent proceeding or in the trial of this or any other action all questions of authenticity, foundation, relevancy, materiality, privilege, and evidentiary admissibility of any information or document provided or identified in these responses; (b) the right to object on any ground to the use or introduction into evidence of any information or document in any subsequent proceeding or in the trial of this or any other action on any ground; and (c) the right to object on any ground at any time to additional discovery.

II. GENERAL OBJECTIONS

Respondent makes the following general objections whether or not separately set forth in response:

1. Impax objects to each Interrogatory to the extent it is vague, ambiguous, overbroad, unduly burdensome, and/or fails to describe the information sought with reasonable particularity.
2. Impax objects to each Interrogatory to the extent it requires the disclosure of information that is neither relevant to the parties' claims or defenses in this action nor reasonably calculated to lead to the discovery of admissible evidence.
3. Impax objects to each Interrogatory to the extent it requires the disclosure of any information that is a matter of public record, or is equally available to Complaint Counsel.

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4. Impax objects to each Interrogatory to the extent it seeks information not in Impax's possession, custody, or control.
5. Impax objects to each Interrogatory to the extent it does not contain reasonable time limits.
6. Impax objects to each Interrogatory to the extent it calls for information that is protected by the attorney-client privilege, the joint prosecution privilege, the joint defense privilege, the work-product doctrine, or any other privileges, protections, or doctrines of similar effect.
7. Impax objects to each Interrogatory to the extent it seeks to impose obligations different from, or in excess of, those required or authorized by the Federal Trade Commission's Rules of Practice or any applicable order or rule of this Court.
8. Impax's discovery and investigation into the matters specified are continuing. Accordingly, Impax reserves its right to supplement, alter, or change its responses and objections to each Interrogatory and to provide additional information that Impax has in its possession, custody, or control at the time the Interrogatories were propounded, in the manner and to the extent required or permitted by the Federal Trade Commission's Rules of Practice.
9. Impax objects to each Interrogatory to the extent it seeks Impax's proprietary, confidential, financial, trade secret, or commercially-sensitive information, the disclosure of which would unduly and improperly invade its protected rights. Impax similarly objects to each Interrogatory to the extent it seeks third-party proprietary, confidential,

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financial, trade secret, or commercially-sensitive information, the disclosure of which could harm third parties' competitive or business positions or result in a breach of Impax's obligation to maintain the confidentiality of such information. Impax will produce such information as necessary, subject to the Protective Order entered by the Court.

10. Impax's responses do not in any way constitute an adoption of Complaint Counsel's purported Definitions of words or phrases. Impax objects to the Definitions to the extent they (i) are unclear, ambiguous, overly broad, or unduly burdensome; (ii) are inconsistent with the ordinary and customary meaning of the words or phrases they purport to define; and/or (iii) seek to impose obligations different from, or in excess of, those created by the Federal Trade Commission's Rules of Practice. Without limiting the generality of this objection, Impax specifically objects to the following:

    A. Impax objects to the definition of the terms "Impax" and "the Company" in Definition 1 to the extent it purports to include third-party "agents," "consultants," "representatives," or "affiliates" on the grounds that the definition is vague, ambiguous, overly broad, and/or unduly burdensome.

    B. Impax objects to the definition of the term "Documents" in Definition 5 to the extent it purports to include "all drafts (whether or not they resulted in a final document), and all copies that differ in any respect from the original," on the grounds that the definition is overly broad and unduly burdensome.

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C. Impax objects to the definition of the term "Endo" in Definition 7 to the extent it purports to include third-party "agents," "consultants," "representatives," or "affiliates" on the grounds that the definition is vague, ambiguous, overly broad, and/or unduly burdensome.

11. To the extent that Impax adopts any term defined by Complaint Counsel, it is adopted solely for convenience in responding to Complaint Counsel's Interrogatories, and Impax does not accept or concede that any of the terms or definitions contained therein are appropriate, descriptive, or accurate.

12. Impax objects to Complaint Counsel's Instructions to the extent that they purport to impose burdens and requirements on Impax that exceed or differ from the requirements of the Federal Trade Commission's Rules of Practice. Without limiting the generality of this objection, Impax specifically objects to the following:

A. Impax objects to Complaint Counsel's Instruction 1 to the extent that it does not contain reasonable time limits.

B. Impax objects to Complaint Counsel's assertion in Instruction 8 that each Interrogatory "is continuing and requires prompt amendment," to the extent it purports to impose duties on Impax beyond that which is required by the Federal Trade Commission's Rules of Practice. Impax will supplement its responses pursuant to the requirements set forth in Rule §3.31(e)(2) of the Federal Trade Commission's Rules of Practice.

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C. Impax objects to Complaint Counsel's Instruction 15 to the extent it requests information that Impax does not have or information that is publicly available or equally accessible by Complaint Counsel.

III. SPECIFIC RESPONSES AND OBJECTIONS

Interrogatory No. 1:

Identify any joint defense or common interest between You and Endo in any actual or potential litigation (including, but not limited to, *FTC v. Endo Pharmaceuticals Inc.*, Case No. 16-cv-01440 (E.D. Pa. filed March 30, 2016), *Endo Pharmaceuticals Inc. v. FTC*, Case No. 16-cv-05600 (E.D. Pa. filed Oct. 16, 2016), and *In re Opana Antitrust Litigation*, Case Nos. 1:14-cv-10150, 1:14-cv-07320, and 15-cv-00269 (N.D. Ill.)), and describe the subject matter and scope of any joint defense or common interest.

Response to Interrogatory No. 1:

Impax objects to Interrogatory No. 1 as vague and overbroad in that it asks whether Impax and Endo may have a "common interest" in any "potential litigation."

Impax further objects to Interrogatory No. 1 to the extent that it requires Impax reveal attorney work product or information that is otherwise privileged.

Impax further objects to this Interrogatory to the extent it requests information regarding the existence or details of any joint defense agreement, joint defense relationship, common interest agreement, or common interest relationship, in any proceedings other than the instant litigation. Neither the fact nor details of any such agreement or relationship (to the extent any exist) are relevant to the allegations in the Complaint, any proposed relief, or Impax's defenses.

Finally, to the extent that Interrogatory No. 1 asks whether Impax has any interest in common with Endo at a theoretical level, Impax objects that responding to Interrogatory No. 1 calls for a legal conclusion and involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under Federal Trade Commission Rule of Practice § 3.35(b)(2), no answer is required until the close of discovery, if at all.

Subject to and without waiving the foregoing objections, Impax responds as follows: Impax has no joint defense or common interest agreement with Endo in this litigation.

Interrogatory No. 2:

Identify all procompetitive justifications and benefits to consumers and the public interest referenced in the Eighth Defense in Your Answer to the Complaint in this case, and explain the factual basis for Your answer to this Interrogatory, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

Response to Interrogatory No. 2:

Impax objects that responding to Interrogatory No. 2 involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under Federal Trade Commission Rule of Practice § 3.35(b)(2), no answer is required until the close of discovery. Impax will supplement its response to Interrogatory No. 2 in due course.

Interrogatory No. 3:

For each procompetitive justification and benefit identified in response to Interrogatory No. 2, explain how the No-AG Provision and the Endo Credit provision contained in the Opana ER Settlement and License Agreement were reasonably necessary to achieve that

benefit, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

Response to Interrogatory No. 3:

Impax objects that responding to Interrogatory No. 3 involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under Federal Trade Commission Rule of Practice § 3.35(b)(2), no answer is required until the close of discovery. Impax will supplement its response to Interrogatory No. 3 in due course.

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Dated: XXXX, 2017

/s/Edward D. Hassi
Edward D. Hassi
Michael E. Antalics
Benjamin J. Hendricks
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1625 Eye Street, NW
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smcintyre@omm.com

Counsel for Respondent Impax Laboratories, Inc.

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CERTIFICATE OF SERVICE

I hereby certify that on XXXXX, 2017, I served the foregoing document on the following counsel via electronic mail:

Markus Meier
Bradley Albert
Daniel Butrymowicz
Nicholas Leefer
Synda Mark
Maren Schmidt
Jaime Towey
Eric Sprague
Chuck Loughlin

Federal Trade Commission
600 Pennsylvania Ave., N.W.
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mmeier @ftc.gov
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cloughlin@ftc.gov

Counsel for Complainant Federal Trade Commission

/s/ Anna M. Fabish
Anna M. Fabish

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Exhibit C

Leefer, Nicholas

From: Fabish, Anna <afabish@omm.com>
Sent: Wednesday, May 24, 2017 10:28 AM
To: Leefer, Nicholas; Hassi, Ted; Antalics, Michael E.; Parker, Richard; McIntyre, Stephen; Hendricks, Benjamin J.; Brogan, Eileen M.
Cc: Meier, Markus H.; Albert, Bradley Scott; Butrymowicz, Daniel W.; Mark, Synda; Schmidt, J. Maren; Towey, Jamie; Sprague, Eric M.; Loughlin, Chuck; Weinstein, Rebecca; Clark, Alexandra
Subject: RE: Docket 9373 - Responses and Objections to First Set of Interrogatories

My May 22nd email below reflects Impax's final position on this issue.

Best,

Anna

From: Leefer, Nicholas [mailto:nleefer@ftc.gov]
Sent: Monday, May 22, 2017 2:14 PM
To: Fabish, Anna; Hassi, Ted; Antalics, Michael E.; Parker, Richard; McIntyre, Stephen; Hendricks, Benjamin J.; Brogan, Eileen M.
Cc: Meier, Markus H.; Albert, Bradley Scott; Butrymowicz, Daniel W.; Mark, Synda; Schmidt, J. Maren; Towey, Jamie; Sprague, Eric M.; Loughlin, Chuck; Weinstein, Rebecca; Clark, Alexandra
Subject: RE: Docket 9373 - Responses and Objections to First Set of Interrogatories

Anna,

Impax's response to CID specification 17 provides only an incomplete answer to Interrogatory Nos. 2 and 3. For example, CID spec 17 only asks for the competitive benefits of the No-AG clause of the settlement agreement, while Interrogatory Nos. 2 and 3 are not so limited. In addition, this response does not resolve our concern of not being able to conduct meaningful discovery related to Impax's affirmative defense because you have reserved the right to add additional purported justifications at the close of discovery.

We also reiterate our position that these are not contention interrogatories. *See Dot Com Entm't Grp., Inc. v. Cyberbingo Corp.*, 237 F.R.D. 43, 44-45 (W.D.N.Y. 2006) (finding that interrogatories asking that Defendants "state the facts which support Defendants' invalidity defense" and "identify the prior art upon which Defendants' prior art defense is predicated" did not "involve an opinion or contention that relates to fact or the application of law to fact" and so were not contention interrogatories) (internal quotations omitted). Interrogatory Nos. 2 and 3 are similar to those the *Cyberbingo* court found should be answered early in discovery because "Defendants are expected to have, even at an early stage, some good faith basis in fact and law for such claim and defense." *Id*. at 45.

Please let us know Impax's final position on these interrogatories by Wednesday, May 24. If we cannot reach an agreement on these issues, we may be forced to seek relief from Judge Chappell.

Best Regards,

Nicholas Leefer
Federal Trade Commission
Bureau of Competition, Health Care Division
202-326-3573
nleefer@ftc.gov

From: Fabish, Anna [mailto:afabish@omm.com]
Sent: Monday, May 22, 2017 11:34 AM
To: Leefer, Nicholas; Hassi, Ted; Antalics, Michael E.; Parker, Richard; McIntyre, Stephen; Hendricks, Benjamin J.; Brogan, Eileen M.
Cc: Meier, Markus H.; Albert, Bradley Scott; Butrymowicz, Daniel W.; Mark, Synda; Schmidt, J. Maren; Towey, Jamie; Sprague, Eric M.; Loughlin, Chuck; Weinstein, Rebecca
Subject: RE: Docket 9373 - Responses and Objections to First Set of Interrogatories

Nicholas -

As discussed during our meet and confer last week regarding the issues you raise below, Impax continues to object to Interrogatories 2 and 3 as contention interrogatories, to which Impax need not respond until the close of discovery, if at all. However, three years ago, Impax identified numerous procompetitive justifications and benefits to consumers in Impax's narrative response to CID Specification 17. As we stated then (subject to and without waiving the objections noted in our narrative responses):

"[T]here are several benefits flowing from the SLA's co-exclusive licensing provisions. Impax and Endo were settling a contested and uncertain patent dispute. Impax's objective was to secure a path to launching and selling generic original Opana ER while neutralizing the risk of patent infringement liability and damages to Endo. Impax naturally preferred to maximize its sales. The co-exclusive licensing provisions helped to serve these ends. Under the collection of terms embodied in the SLA, Impax received, among other things, a license and covenants that permitted Impax to manufacture and sell generic original Opana ER free from patent infringement risk to Endo earlier than Impax likely would have been able to achieve through other means. Specifically, the SLA permitted Impax to introduce generic original Opana ER no later than January 2013—earlier than Impax likely would have otherwise entered, before the patents that were the subject of the parties' litigation were set to expire, and before patents subsequently issued to or obtained by Endo are set to expire. Had Impax not settled the litigation on the material terms it did, Impax would likely be embroiled in patent litigation with Endo even today (as are other generic companies), rather than having the freedom to operate it obtained and selling its generic version of original Opana ER. The SLA agreement increased competition and directly benefited consumers."

Impax reserves the right to supplement this prior answer in responding to Interrogatories 2 and 3 at the close of discovery.

With respect to Interrogatory 1, Impax served a supplemental response to this interrogatory earlier today.

Best,

Anna

O'Melveny

Anna M. Fabish
Counsel
afabish@omm.com
O: +1-213-430-7512

O'Melveny & Myers LLP
400 South Hope Street, 18th Floor
Los Angeles, CA 90071
Website | LinkedIn | Twitter

From: Leefer, Nicholas [mailto:nleefer@ftc.gov]
Sent: Tuesday, May 09, 2017 12:05 PM
To: Fabish, Anna; Hassi, Ted; Antalics, Michael E.; Parker, Richard; McIntyre, Stephen; Hendricks, Benjamin J.; Brogan, Eileen M.
Cc: Meier, Markus H.; Albert, Bradley Scott; Butrymowicz, Daniel W.; Mark, Synda; Schmidt, J. Maren; Towey, Jamie; Sprague, Eric M.; Loughlin, Chuck; Weinstein, Rebecca
Subject: RE: Docket 9373 - Responses and Objections to First Set of Interrogatories

Anna,

We would like to meet and confer with you regarding Impax's responses to our First Set of Interrogatories. Please let us know your availability this week or next for a call. In the hopes of having a quick and productive conversation, these are the issues we would like to discuss:

1. **Interrogatory No. 1**: We disagree with Impax's objections. First, the existence of a common interest or joint defense, in and of itself, is not privileged or work product. Second, as we have explained, the existence—or lack thereof—of a common interest or joint defense with respect to the agreements at issue in this case already came up as a point of contention during the case scheduling conference, and bears on various aspects of the case. Third, we are only interested in a common interest or joint defense that would give rise to an assertion of privilege or work product covering documents or communications shared between Endo and Impax in the identified proceedings, rather than "any interest in common at a theoretical level." We ask that Impax provide this information.
2. **Interrogatory No. 2**: We understand that Impax is not required to respond to contention interrogatories until the close of discovery. However, this interrogatory does not solely request "an opinion or contention that relates to fact or the application of law to fact." In particular, the language highlighted below seeks clarification and a clearer articulation of one of Impax's defenses. This information is necessary to conduct discovery relevant to Impax's defense, so an answer after the close of discovery would be untimely. We ask that Impax provide a substantive answer to the highlighted section of this interrogatory at this time.
    a. Identify all procompetitive justifications and benefits to consumers and the public interest referenced in the Eighth Defense in Your Answer to the Complaint in this case, and explain the factual basis for Your answer to this Interrogatory, including identifying all facts and documents You rely on in Your answer to this Interrogatory.
3. **Interrogatory No. 3**: As above, this interrogatory contains non-contention portions. The language highlighted below seeks clarification and clearer articulation of Impax's defenses. This information is necessary to conduct discovery relevant to Impax's defenses, so an answer after the close of discovery would be untimely. We ask that Impax provide a substantive answer to the highlighted section of this interrogatory at this time.
    a. For each procompetitive justification and benefit identified in response to Interrogatory No. 2, explain how the No-AG Provision and the Endo Credit provision contained in the Opana ER Settlement and License Agreement were reasonably necessary to achieve that benefit, including identifying all facts and documents You rely on in Your answer to this Interrogatory.

In addition, we would like to follow up on our previous discussions related to the use of search terms to locate documents belonging to Joe Camargo, John Anthony, and Mark Donohue; as well as documents postdating Impax's CID production. Based on your April 27 email, we understood that you were going to discuss our search proposal with Impax, but we have not yet heard back. Please let us know Impax's position on running the searches we proposed by Friday, May 12. Thank you.

Best Regards,

Nicholas Leefer

Federal Trade Commission
Bureau of Competition, Health Care Division
202-326-3573
nleefer@ftc.gov

From: Fabish, Anna [mailto:afabish@omm.com]
Sent: Friday, May 05, 2017 3:17 PM
To: Leefer, Nicholas; Meier, Markus H.; Albert, Bradley Scott; Butrymowicz, Daniel W.; Mark, Synda; Schmidt, J. Maren; Towey, Jamie; Sprague, Eric M.; Loughlin, Chuck; Weinstein, Rebecca
Cc: Hassi, Ted; Antalics, Michael E.; Parker, Richard; McIntyre, Stephen; Hendricks, Benjamin J.; Brogan, Eileen M.
Subject: Docket 9373 - Responses and Objections to First Set of Interrogatories

Counsel -

Attached are Respondent's Responses and Objections to Complaint Counsel's First Set of Interrogatories.

Best,

Anna

O'Melveny

Anna M. Fabish
Counsel
afabish@omm.com
O: +1-213-430-7512

O'Melveny & Myers LLP
400 South Hope Street, 18th Floor
Los Angeles, CA 90071
Website | LinkedIn | Twitter

Notice of Electronic Service

I hereby certify that on June 01, 2017, I filed an electronic copy of the foregoing CC Motion to Compel Response to Interrogatories, with:

D. Michael Chappell
Chief Administrative Law Judge
600 Pennsylvania Ave., NW
Suite 110
Washington, DC, 20580

Donald Clark
600 Pennsylvania Ave., NW
Suite 172
Washington, DC, 20580

I hereby certify that on June 01, 2017, I served via E-Service an electronic copy of the foregoing CC Motion to Compel Response to Interrogatories, upon:

Bradley Albert
Attorney
Federal Trade Commission
balbert@ftc.gov
Complaint

Daniel Butrymowicz
Attorney
Federal Trade Commission
dbutrymowicz@ftc.gov
Complaint

Nicholas Leefer
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Complaint

Lauren Peay
Attorney
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Complaint

James H. Weingarten
Attorney
Federal Trade Commission
jweingarten@ftc.gov
Complaint

I hereby certify that on June 01, 2017, I served via other means, as provided in 4.4(b) of the foregoing CC Motion to Compel Response to Interrogatories, upon:

Markus Meier
Attorney
Federal Trade Commission
mmeier@ftc.gov
Complaint

Ted Hassi
Attorney
O'Melveny & Myers LLP
ehassi@omm.com
Respondent

Nicholas Leefer
Attorney

EXHIBIT C

UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	DOCKET NO. 9373
Respondent.	)	

SECOND REVISED SCHEDULING ORDER

Pursuant to the Order Granting Joint Motion to Extend Discovery Schedule, issued on June 19, 2017, the remaining deadlines set forth in the Scheduling Order issued in this case on February 17, 2017 are hereby revised. All other provisions remain of the Scheduling Order, as supplemented by the Revised Scheduling Order issued on April 24, 2017 remain in effect, and are further supplemented herein (*see* prehearing conference instructions, below).

July 24, 2017	-	Deadline for issuing requests for admissions, except for requests for admissions for purposes of authenticity and admissibility of exhibits.
July 28, 2017	-	Respondent's Counsel provides expert witness list.
August 11, 2017	-	Close of discovery, other than discovery permitted under Rule 3.24(a)(4), depositions of experts, and discovery for purposes of authenticity and admissibility of exhibits.
August 18, 2017	-	Deadline for Complaint Counsel to provide expert witness reports.
September 5, 2017	-	Deadline for Respondent's Counsel to provide expert witness reports (to be provided by 4 p.m. ET). Respondent's expert report shall include (without limitation) rebuttal, if any, to Complaint Counsel's expert witness report(s).

September 13, 2017	-	Complaint Counsel provides to Respondent's Counsel its final proposed witness and exhibit lists, including depositions, copies of all exhibits (except for demonstrative, illustrative or summary exhibits and expert related exhibits), Complaint Counsel's basis of admissibility for each proposed exhibit, and a brief summary of the testimony of each witness. Complaint Counsel serves courtesy copies on ALJ of its final proposed witness and exhibit lists, its basis of admissibility for each proposed exhibit, and a brief summary of the testimony of each witness, including its expert witnesses.
September 20, 2017	-	Complaint Counsel to identify rebuttal expert(s) and provide rebuttal expert report(s). Any such reports are to be limited to rebuttal of matters set forth in Respondent's expert reports. If material outside the scope of fair rebuttal is presented, Respondent will have the right to seek appropriate relief (such as striking Complaint Counsel's rebuttal expert reports or seeking leave to submit surrebuttal expert reports on behalf of Respondent).
September 26, 2017	-	Respondent's Counsel provides to Complaint Counsel its final proposed witness and exhibit lists, including depositions, copies of all exhibits (except for demonstrative, illustrative or summary exhibits and expert related exhibits), Respondent's basis of admissibility for each proposed exhibit, and a brief summary of the testimony of each witness. Respondent's Counsel serves courtesy copies on ALJ its final proposed witness and exhibit lists, its basis of admissibility for each proposed exhibit, and a brief summary of the testimony of each witness, including its expert witnesses.
September 27, 2017	-	Parties that intend to offer confidential materials of an opposing party or non-party as evidence at the hearing must provide notice to the opposing party or non-party, pursuant to 16 C.F.R. § 3.45(b).[1] *See* Additional Provision 7.

[1] Appendix A to Commission Rule 3.31, the Standard Protective Order, states that if a party or third party wishes *in camera* treatment for a document or transcript that a party intends to introduce into evidence, that party or third party shall file an appropriate motion with the Administrative Law Judge within 5 days after it receives notice of a party's intent to introduce such material. Commission Rule 3.45(b) states that parties who seek to use material obtained from a third party subject to confidentiality restrictions must demonstrate that the third party has been given at least 10 days' notice of the proposed use of such material. To resolve this apparent conflict, the Scheduling Order requires that the parties provide 10 days' notice to the opposing party or third parties to allow for the filing of motions for *in camera* treatment.

October 2, 2017	-	Deadline for depositions of experts (including rebuttal experts) and exchange of expert related exhibits.
October 4, 2017	-	Deadline for filing motions *in limine* to preclude Admission of evidence. *See* Additional Provision 9.
October 4, 2017	-	Exchange and serve courtesy copy on ALJ objections to final proposed witness lists and exhibit lists. The Parties are directed to review the Commission's Rules on admissibility of evidence before filing objections to exhibits.
October 10, 2017	-	Deadline for filing motions for *in camera* treatment of proposed trial exhibits.
October 10, 2017	-	Complaint Counsel files pretrial brief supported by legal authority.
October 10, 2017	-	Deadline for filing responses to motions *in limine* to preclude admissions of evidence.
October 11, 2017	-	Exchange proposed stipulations of law, facts, and authenticity.
October 13, 2017	-	Deadline for filing responses to motions for *in camera* treatment of proposed trial exhibits.
October 17, 2017	-	Respondent's Counsel files pretrial brief supported by legal authority.
October 19, 2017	-	Final prehearing conference to begin at 10:00 a.m. in FTC Courtroom, Room 532, Federal Trade Commission Building, 600 Pennsylvania Avenue, NW, Washington, DC 20580. The parties shall meet and confer prior to the prehearing conference regarding trial logistics and proposed stipulations of law, facts, and authenticity of exhibits. To the extent the parties have agreed to stipulate to any issues of law, facts, and/or authenticity of exhibits, the parties shall prepare a list of such stipulations and submit a copy of the stipulations to the ALJ one business day prior to the conference. At the conference, the parties' list of stipulations shall be marked as "JX1" and signed by each party, and the list shall be offered into evidence as a joint exhibit. No signature by the ALJ is required. Any subsequent stipulations may be offered as agreed by the parties. Counsel may present any objections to the final proposed witness lists and exhibits. Trial exhibits will be admitted or excluded to

the extent practicable. To the extent the parties agree to the admission of each other's exhibits, the parties shall prepare a list identifying each exhibit to which admissibility is agreed, marked as "JX2" and signed by each party, which list shall be offered into evidence as a joint exhibit. No signature by the ALJ is required.

At the final prehearing conference, counsel will be required to introduce all exhibits they intend to introduce at trial and provide the exhibits to the court reporter. The parties shall confer and shall eliminate duplicative exhibits in advance of the final prehearing conference and, if necessary, during trial. For example, if CCX 100 and RX 200 are different copies of the same document, only one of those documents shall be offered into evidence. The parties shall agree in advance as to which exhibit number they intend to use. Counsel shall contact the court reporter regarding submission of exhibits.

October 24, 2017 - Commencement of Hearing, to begin at 10:00 a.m. in FTC Courtroom, Room 532, Federal Trade Commission Building, 600 Pennsylvania Avenue, NW, Washington, DC 20580.

ORDERED:

D. Michael Chappell
Chief Administrative Law Judge

Date: June 19, 2017

EXHIBIT D

REDACTED IN ENTIRETY

EXHIBIT E

REDACTED IN ENTIRETY

EXHIBIT F

REDACTED IN ENTIRETY

EXHIBIT G

REDACTED IN ENTIRETY

EXHIBIT H

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. IMPAX LABORATORIES, INC. Defendant.	C.A. No. 09-831 (KSH) (PS)
ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. SANDOZ, INC. Defendant.	C.A. No. 09-836 (KSH) (PS)
ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO., Plaintiffs, v. BARR LABORATORIES, INC. Defendant.	C.A. No. 09-838 (KSH) (PS)

ORDER ON CLAIM CONSTRUCTION

This matter having been opened to the Court by the parties and by the Scheduling Orders of United States Magistrate Judge Patty Shwartz, and the Court having considered the parties' respective submissions and argument in support of their proposed constructions of the disputed

terms of U.S. Patent No. 5,662,933 ("the '933 Patent") and U.S. Patent No. 5,948,456 ("the '456 Patent"), and the Court having conducted a Markman Hearing on December 21, 2009, and a continuation of said Hearing on March 19, 2010, and for good cause shown,

IT IS on this 30th day of March, 2010,

HEREBY ORDERED that pursuant to the stipulation and agreement of the parties to these matters, and solely for purposes of claim construction in the above-captioned actions, the Court construes the following disputed terms in the asserted claims of the '933 Patent as follows:

1. The term "gum" as used in the claims of the '933 Patent means "a plant or microbial polysaccharide or its derivatives that when dispersed in water at low dry substance content swells to produce gels or highly viscous dispersions or solutions."

2. The term "heteropolysaccharide" as used in the claims of the '933 Patent means "a water soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having water-wicking and thickening properties."

3. The term "homopolysaccharide" as used in the claims of the '933 Patent means "a polysaccharide composed of only one type of monosaccharide, and also galactomannans."

IT IS FURTHER ORDERED that for the reasons set forth on the record by the Court at the continuation of the Markman Hearing held on March 19, 2010, the Court construes the following disputed terms in the asserted claims of the '933 Patent and the '456 Patent as follows:

1. The term "medicament plasma concentration-time curve" as used in the claims of the '933 Patent means "a curve representing the relationship of medicament plasma concentration versus time in a study population."

2. The term "from about 25% to about 50%" as used in the claims of the '933 and '456 Patents means "from 24.5% to 50.4%."

3. The term "sustained release" as used in the claims of the '933 and '456 Patents means "the active medicament is released at a controlled rate such that therapeutically beneficial levels of the medicament are maintained over a period of at least 12 hours."

4. The term "hydrophobic material" as used in the claims of the '933 and '456 Patents means "a material which is effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix."

/s/ Katharine S. Hayden
Katharine S. Hayden, U.S.D.J.

EXHIBIT I

REDACTED IN ENTIRETY

EXHIBIT J

REDACTED IN ENTIRETY

EXHIBIT K

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and MALLINCKRODT LLC, Plaintiffs, v. ACTAVIS INC., ACTAVIS SOUTH ATLANTIC LLC, ACTAVIS PHARMA, INC., ACTAVIS ELIZABETH LLC, ACTAVIS HOLDCO U.S., INC., and TEVA PHARMACEUTICALS USA, INC. Defendants.	Civil Action No. 14-1381-RGA

TRIAL OPINION

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Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

August 30, 2017

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs brought this patent infringement action against two Actavis defendants on November 7, 2014, alleging that they had infringed U.S. Patent No. 8,871,779 ("the '779 patent") by filing Abbreviated New Drug Application ("ANDA") No. 20-3930 seeking to enter the market with a generic version of Plaintiffs' Opana ER product, which is an extended-release oxymorphone tablet. (D.I. 1). On the same day, Plaintiffs also filed suit separately against Defendant Teva, alleging infringement of the '779 patent through Defendant Teva's filing of ANDA No. 20-4324, which also sought approval for a generic version of extended-release oxymorphone tablets. (Civ. Act. No. 14-1389, D.I. 1). The parallel case against Defendant Teva proceeded to a bench trial in July 2016 at which Defendant Teva stipulated to infringement but asserted several defenses, including invalidity on the basis of obviousness. (Civ. Act. No. 14-1389, D.I. 192 at 6). On October 7, 2016, the Court issued a trial opinion holding that Defendant Teva had not proved by clear and convincing evidence that any of the asserted claims of the '779 patent were invalid. (*Id.* at 30).

On October 31, 2016, the Actavis Defendants filed an amended disclosure statement, notifying the Court that they had been acquired by Defendant Teva and that, as a result, the Actavis Defendants operate as wholly-owned subsidiaries of Defendant Teva. (D.I. 125 at 1). In light of this disclosure, Plaintiffs requested that the schedule in the instant case be extended so that they could amend their complaint to name Teva as a defendant, conduct additional discovery related to the acquisition, and pursue summary judgment on the basis of res judicata and/or collateral estoppel. (D.I. 128). On December 8, 2016, I issued an order denying the request to postpone the trial, but allowing Plaintiffs to file an amended complaint and granting Plaintiffs a two-month period in which to conduct fact discovery related to the acquisition. (D.I. 139).

Plaintiffs filed an amended complaint naming five Actavis entities and Teva as defendants, which included a new Count VII seeking a declaratory judgment that all defendants were precluded from litigating the validity of the '779 patent on the basis of the Court's decision in Civ. Act. No. 14-1389. (D.I. 140). The Actavis Defendants and Defendant Teva separately moved to dismiss Count VII on the bases that Plaintiffs had not plead privity of the parties or identical causes of action and/or issues. (D.I. 147). The Court granted the motion to dismiss Count VII as to all defendants on the basis that claim and/or issue preclusion did not provide an independent basis for relief. (D.I. 172).

This case concerns two molecules. The first is 14-hydroxydihydromorphinone, also referred to as "oxymorphone" or "oxymorphone HCl."[1] The other is 14-hydroxymorphinone, also referred to as "oxymorphone ABUK." ABUK, which stands for alpha,beta-unsaturated ketones, is a term used to describe a double bond between the alpha and beta carbons in a ketone. (Trial Transcript ("Tr.") at 37:14-38:6). The difference between oxymorphone and oxymorphone ABUK, then, is that oxymorphone is saturated, meaning there is only a single bond between the alpha and beta carbons. Oxymorphone ABUK is considered a precursor of oxymorphone because it can be made into oxymorphone by adding a hydrogen, resulting in a single bond. (Tr. 76:19-79:19).

Oxymorphone is an opioid that has been known and used as a pain reliever for over fifty years. (Tr. 34:8-14). Prior to 2002, manufacturers of oxymorphone were aware of the impurity now known as oxymorphone ABUK. (Tr. 222:12-21). During the period before 2002, manufacturers regularly sold oxymorphone HCl with oxymorphone ABUK levels in the range of

[1] Oxymorphone and oxymorphone HCl are actually different compounds, in that the latter is a salt formed when chloride is added. In this opinion, however, they are used interchangeably, as the key distinction in this case is between oxymorphone ABUK and oxymorphone without the ABUK double bond.

thousands of parts per million ("ppm"). (Tr. 329:7-14). In 2002, the FDA informed Mallinckrodt and several other manufacturers that it was concerned about the levels of ABUK in certain products. (Tr. 223:7-225:10). The FDA informed Mallinckrodt that it intended to impose limits on the levels of ABUK, and that it might require limits as low as 0.001 percent (or 10 ppm) ABUK. (*Id.*). In 2004, the FDA mandated that opioid manufacturers lower the levels of ABUK in opioid pharmaceuticals to less than 10 ppm. (Tr. 224:16-19). For the purposes of this opinion, oxymorphone HCl which contains less than 10 ppm of oxymorphone ABUK—and thus complies with FDA's mandate—will be referred to as "low-ABUK oxymorphone."

In 2005, Mallinckrodt succeeded in reaching the low ABUK levels mandated by the FDA for oxymorphone HCl. Mallinckrodt applied for a patent on its new low-ABUK oxymorphone product. The application ultimately issued as the '779 patent. The asserted claims of the '779 patent[2] are all product claims directed to low-ABUK oxymorphone.

Independent claim 1 of the '779 patent reads:

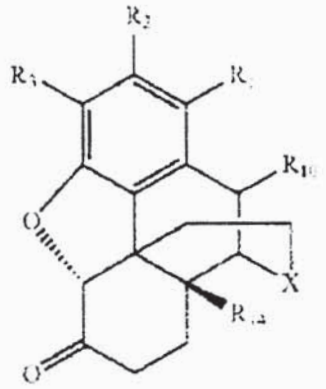
> A hydrochloride salt of oxymorphone comprising less than 0.001% of 14-hydroxymorphinone.

('779 patent, claim 1). Dependent claim 2 limits the level of 14-hydroxymorphinone to less than 0.0005%. (*Id.* at claim 2). Dependent claim 3 claims a pharmaceutically acceptable form of the hydrochloride salt in claim 1. (*Id.* at claim 3). Independent claim 4 reads:

> A hydrochloride salt of a morphinan-6-one compound corresponding to Formula (2):

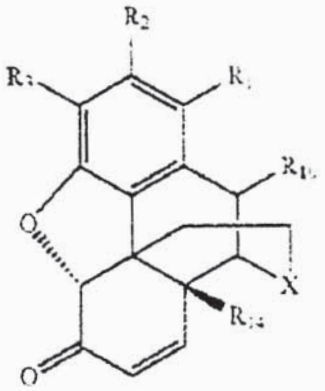
[2] Plaintiffs assert that all six claims of the '779 patent are infringed.

(2)



comprising less than 0.001% measured by HPLC of an α,β-unsaturated ketone compound corresponding to Formula (3):

(3)



wherein the morphinan-6-one compound is oxymorphone and wherein X is —N(R_{17})—;
R_1 and R_2 are hydrogen;
R_3 is hydroxy;
R_{10} is hydrogen;
R_{14} is hydroxy; and
R_{17} is methyl.

(*Id.* at claim 4). Dependent claim 5 limits the level of 14-hydroxymorphinone to 0.0005%. (*Id.* at claim 5). Dependent claim 6 claims a pharmaceutical formulation of the oxymorphone chloride in claim 4. (*Id.* at claim 6).

The Court held a bench trial on February 21-23, 2017. The Actavis Defendants concede that their proposed products meet all limitations of the '779 patent. (D.I. 170-1 at 2). The Actavis Defendants argue that the '779 patent is invalid as obvious, anticipated, and lacking written description.[3]

I. COLLATERAL ESTOPPEL

Plaintiffs have raised, and I have rejected, a variety of preclusion arguments twice since Defendants notified the court of Teva's acquisition of Actavis. (D.I. 128, 139, 140, 171). In post-trial briefing, Plaintiffs again assert that all Defendants are collaterally estopped from challenging validity on the basis of the judgment entered against Teva in Civ. Act. No. 14-1389.

Collateral estoppel requires a finding that "(1) the identical issue was previously adjudicated; (2) the issue was actually litigated; (3) the previous determination was necessary to the decision; and (4) the party being precluded from relitigating the issue was fully represented in the prior action." *Raytech Corp. v. White*, 54 F.3d 187, 190 (3d Cir. 1995).

Plaintiffs argue that because obviousness was tried in the earlier case and obviousness is "the only remaining validity issue" in the instant case, the identical issue element of collateral estoppel is met. (D.I. 199 at 11). Plaintiffs assert that this is the only dispute as to whether collateral estoppel applies to bar Defendant Teva from challenging the validity of the '779 patent. (*Id.*). According to Plaintiffs, "validity is a single, overarching issue for collateral estoppel purposes." (*Id.* at 12).

Defendants first respond that Defendant Teva did not contest validity at trial. (D.I. 216 at 9). Plaintiffs seize on this as a purported admission that mandates judgment as a matter of law of

[3] Plaintiffs have also filed a Motion for Leave to File a 5-Page Surreply in Response to New Arguments in Defendants' Post-Trial Reply Brief. (D.I. 228). Because I find that Defendants have raised at least one new argument in their reply brief, I will grant Plaintiffs' motion and consider the arguments made in the surreply.

non-obviousness against Defendant Teva. (D.I. 220 at 6). I disagree. The ANDA at issue in this case, the filing of which represents the act of infringement providing the jurisdictional basis for this suit, was filed not by Defendant Teva, but by the Actavis Defendants. Therefore, Plaintiffs' argument that Defendant Teva is collaterally estopped from doing anything first requires a finding that Defendant Teva and the Actavis Defendants are the same party.

I do not think Plaintiffs have demonstrated the requisite privity between Defendant Teva and the Actavis Defendants to invoke collateral estoppel to preclude any Defendant from challenging the validity of the '779 patent. The Actavis Defendants were not a party to the earlier suit, were not represented in that suit, and did not participate in that litigation. Furthermore, the ANDA that provides the jurisdictional basis for this suit is different from the ANDA being challenged in the previous suit and each of these two ANDAs were filed by different parties. I fail to see how I could preclude the Actavis Defendants from challenging the validity of this patent on the basis that a different party, who happened to acquire the Actavis Defendants long after this suit was filed, previously litigated the validity of the patent. This is not a case of Defendant Teva getting a second opportunity to challenge validity. Rather, it is a case of the Actavis Defendants getting their own opportunity to litigate their own suit predicated on their own ANDA. I hold that the Actavis Defendants are not collaterally estopped from litigating the validity of the '779 patent. As Defendant Teva did not present evidence at trial challenging the validity of the '779 patent, there is no reason to apply collateral estoppel as to Defendant Teva.

II. DATE OF INVENTION

Before I can determine whether Defendants' asserted references are prior art to the '779 patent, I must first determine the invention date of each of the claims. The provisional

application which ultimately matured into the '779 patent was filed on March 2, 2006, and this is the priority date referenced on the face of the patent. At trial, Plaintiffs presented evidence they claim establishes that the invention was conceived of and reduced to practice no later than February 2, 2005. (Tr. 616:18-618:11). As part of their invalidity case, Defendants presented the Casner reference. (Tr. 119:16-121:6). Casner is a U.S. Patent Application filed on September 23, 2005. (DTX-008). Plaintiffs do not dispute that Casner qualifies as prior art unless Plaintiffs can establish conception and reduction to practice prior to September 23, 2005.

As an initial matter, I note that Defendants incorrectly state the burden of proof for establishing conception and reduction to practice. Defendants assert that it is the Plaintiffs' burden to prove the earlier priority date. (D.I. 201 at 42). This is incorrect. Defendants rely on *PowerOasis* as support for the proposition that the "burden is on patentee to prove earlier priority date once prior art is identified." (*Id.* (citing *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305-06 (Fed. Cir. 2008))). Defendants misstate the Federal Circuit's holding in *PowerOasis*. The court stated that once the challenger had "established by clear and convincing evidence" that the asserted reference qualified as prior art, "the burden was on [Plaintiff] to come forward with evidence to the contrary." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305 (Fed. Cir. 2008). As the court later clarified, *PowerOasis* does not mean the patentee has the burden of persuasion; rather, the patentee has only a burden of production. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1329 (Fed. Cir. 2008). As the court explained,

> once a challenger (the alleged infringer) has introduced sufficient evidence to put at issue whether there is prior art alleged to anticipate the claims being asserted, prior art that is dated earlier than the apparent effective date of the asserted patent claim, the patentee has the burden of going forward with evidence and argument to the contrary

Id. Once Plaintiffs meet their burden of production, the burden shifts back to Defendants to

prove by clear and convincing evidence that Plaintiffs are not entitled to the earlier date of invention. *Id.* at 1327-28.

Defendants do not contest conception, but, rather, contend only that Plaintiffs did not establish reduction to practice by February 2, 2005. (D.I. 201 at 42). Reduction to practice is a question of law "based on subsidiary factual findings." *Teva Pharm. Indus. v. AstraZeneca Pharm. LP*, 661 F.3d 1378, 1381 (Fed. Cir. 2011). Reduction to practice requires the inventor demonstrate that he "(1) constructed an embodiment or performed a process that met all the claim limitations and (2) determined that the invention would work for its intended purpose." *Teva Pharm.*, 661 F.3d at 1383. "An inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice." *Id.*

As to the chemical composition claims, claims 1, 2, 4, and 5, Defendants argue that Plaintiffs did not have in February 2005 "a workable invention that was suitable for its intended purpose of reducing ABUK levels in oxymorphone HCl to less than 10 or less than 5 ppm." (D.I. 201 at 43). At trial, Plaintiffs presented the results of experiments designed "to remove the oxymorphone ABUK." (Tr. 362:8-22). The analysis Plaintiffs presented was dated February 2, 2005. (Tr. 364:14-22; JTX-23 at 108). Plaintiffs' expert, Dr. Buehler, described experiments and analysis of a research sample which were recorded in dated and signed lab notebooks, the results of which showed "that the sample had less than five parts per million of the ABUK in question." (Tr. 362:23-365:1; PTX-223 at 6; JTX-23 at 106, 108).

Dr. Buehler reached this conclusion by analyzing the results of the experiments in conjunction with his knowledge of the sensitivity of the instrument used to measure the ABUK impurities. The lab notebook Plaintiffs presented states that no ABUK was detected. (JTX-23 at 108). Plaintiffs presented evidence that the mass spectrometer instrument used to perform the

analysis could detect ABUK levels at least as low as five ppm. (Tr. 477:8-14, JTX-52 at MAL-OPA0043288-290). Plaintiffs also presented additional validation studies confirming the sensitivity of the instrument and also confirming the ABUK levels in the research sample were less than five ppm. (Tr. 480:20-482:20; JTX-52 at MAL-OPA0043281, MAL-OPA0043290).

At trial, Defendants attempted to rebut this evidence by presenting calculations made by their expert, Dr. Gokel. (Tr. 185:18-186:21). Dr. Gokel concluded that the data Plaintiffs rely on to show that they produced a sample of oxymorphone with less than five ppm of ABUK impurities was unreliable. (*Id.*). Plaintiffs countered by showing that Dr. Gokel had made an error in his calculations and that the same calculations made without the error lead to the conclusion that the data was, in fact, reliable. (Tr. 625:23-628:24). Defendants chose not to rebut this testimony and appear to have abandoned their argument that the data from these experiments were unreliable.

Instead, Defendants assert that the experiments Plaintiffs rely on were unreliable because these experiments used a "decomposed sample of sodium hydrosulfide" and were later abandoned as being "unworkable." (D.I. 201 at 43). I am not persuaded. The decomposed sodium hydrosulfide contained a different compound, bisulfite, which is actually responsible for lowering ABUK levels. (D.I. 215 at 18). Plaintiffs do not contest the fact that bisulfite is the key to lowering ABUK in oxymorphone, nor do they contest the fact that the experiments they rely on used what the experimenters believed to be sodium hydrosulfite. (Tr. 372:15-374:12; D.I. 215 at 18). Plaintiffs presented expert testimony, supported by lab notebooks detailing experiments and analysis, that supports a conclusion that the inventors knew, at least as early as 2004, that bisulfite was the active agent in lowering ABUK. (Tr. 367:7-369:6; 408:4-22). I think this is sufficient to establish that the inventors had produced oxymorphone HCl with less

than five ppm of oxymorphone ABUK and knew how to reproduce that result. I find that the date of invention for claims 1, 2, 4, and 5 of the '779 patent is February 2, 2005.

Claims 3 and 6 of the '779 patent claim "[a] pharmaceutically acceptable form" and "[a] pharmaceutical formulation" of oxymorphone HCl, respectively. Defendants argue that even if Plaintiffs establish a date of invention of February 2, 2005 for the low-ABUK oxymorphone HCl, claims 3 and 6 require additional elements and Plaintiffs have not shown that "their crude sample of oxymorphone HCl" met those additional limitations. (D.I. 201 at 44). Plaintiffs counter that they presented evidence that the February 2, 2005 sample "met FDA purity requirements" for an active pharmaceutical ingredient. (D.I. 215 at 19). I think this is sufficient. "Reduction to practice . . . does not require actual use, but only a reasonable showing that the invention will work to overcome the problem it addresses." *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994). Pharmaceutical formulations involving oxymorphone HCl existed in the art prior to 2005. The novelty of Plaintiffs' invention lies only in the reduced levels of ABUK impurities. Plaintiffs established that they possessed the low-ABUK oxymorphone HCl of sufficient purity for use in a pharmaceutical formulation on February 2, 2005. I find this is sufficient to establish an invention date of February 2, 2005 for claims 3 and 6 of the '779 patent.

III. OBVIOUSNESS

Defendants argue that claims 1-6 of the '779 patent are invalid as obvious over the prior art. Specifically, Defendants argue that a person of ordinary skill in the art would have been able to use routine methods known in the art to produce low-ABUK oxymorphone at the levels required by the FDA mandate. (*Id.* at 21). Defendants present three "commonplace organic techniques" that they contend could be performed by "any graduate student" to produce low-ABUK oxymorphone: 1) catalytic hydrogenation of the ABUK impurities; 2) sulfur addition to

separate out the ABUK impurities; and 3) O-demethylation of low-ABUK oxycodone into low-ABUK oxymorphone. (*Id.*).

A. Legal Standard

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1359-60 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1370 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). Secondary considerations of nonobviousness are important because they "serve as insurance against the insidious attraction of the siren hindsight…." *W.L. Gore & Assocs., Inc. v.*

Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

A patentee is not required to present evidence of secondary considerations. *See Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1101 (Fed. Cir. 2015). That said, if the patent challenger establishes a prima facie case of obviousness, "the patentee would be well advised to introduce evidence sufficient to rebut that of the challenger." *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007)). There must be enough evidence, however, for a finding that a given secondary consideration exists by a preponderance of the evidence. *See Apple, Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016) (en banc). If there is, then the probative value of each secondary consideration will be considered in light of the evidence produced. That does not mean, though, that the burden of persuasion on the ultimate question of obviousness transfers to the proponent of the secondary consideration. *Pfizer, Inc.*, 480 F.3d at 1359. That burden stays always with the patent challenger. *Id.* at 1359–60.

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

B. Findings of Fact

1. The level of ordinary skill in the art is either (1) a person with a Ph.D. in organic

chemistry, medicinal chemistry, or a closely related field, and several years of experience in organic synthesis; or (2) a person with a lesser degree in one of these fields, but commensurately greater experience.

2. Casner and the FDA communications are not prior art.

3. Weiss, Chapman, and Rapoport are prior art.

4. Weiss, Chapman, and Rapoport do not teach a person of ordinary skill in the art how to produce low-ABUK oxymorphone.

5. There was no simultaneous invention of low-ABUK oxymorphone.

6. Low-ABUK oxymorphone would not have been obvious to a person of ordinary skill in the art.

C. Conclusions of Law

1. Scope and Content of the Prior Art

i. The FDA Communications

Defendants offer as prior art three documents that represent confidential communications between the FDA and Mallinckrodt, Noramco, and Johnson Matthey. (DTX-242, 138, 134). These communications summarize meetings held between the FDA and each of these companies at which the parties discussed the FDA's mandate that ABUK impurities in oxycodone and oxymorphone be reduced to less than ten ppm. Defendants contend that these private, confidential communications qualify as § 102(b) prior art "because they were disseminated to the interested public." (D.I. 219 at 6).[4] I disagree. To establish that these documents are prior art,

[4] Defendants also argue that the mandate qualifies as prior art under §§ 102(a) & (f) because "the inventors obtained the concept of low-ABUK oxymorphone from the FDA communication before they did any of their own work." (D.I. 219 at 6). I am not persuaded. If someone declares a desire to have a product that has a particular characteristic, but does nothing to provide any teachings on how to achieve that goal, that person has not contributed to the prior art. Defendants additionally point to the court's discussion of the FDA mandate in a different suit as evidence that these communications are § 102(b)

Defendants must prove, by clear and convincing evidence, facts showing that the documents meet the requirements of § 102(b). *N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 936 (Fed. Cir. 1990). Defendants established only that confidential communications were sent to three interested parties; this is not sufficient to make the documents "generally available" as required for them to be § 102(b) prior art. *Id.*

Even if I were to find these communications to qualify as prior art, their relevance is dubious at best. At most, these communications disclose a directive from the FDA that ABUK impurities in oxycodone and oxymorphone be reduced. These communications do not disclose how to achieve this result, nor do they disclose that this result had ever been achieved in the past. The focus of the communications is on the reason for the mandate, the mutagenic properties of ABUK impurities, and discussions of how the FDA would assess the impurity levels. There is simply no disclosure of anything substantive relevant to obviousness in these communications.

ii. Casner

The parties dispute whether Casner is prior art. Casner is a U.S. Patent Application filed on September 23, 2005. (DTX-8 at cover). Since I have already determined that all of the claims of the '779 patent are entitled to an invention date of February 2, 2005, I find that Casner does not qualify as prior art.

iii. Weiss

Weiss generally describes the process of hydrogenating oxymorphone ABUK, thereby converting it into oxymorphone HCl. (JTX-3). Weiss does not provide all of the reaction conditions required to reproduce the described reaction. (Tr. 540:4-14; *see also* JTX-3 at p. 1507). Specifically, Weiss lacks details about hydrogen pressure, amount of acid, amount and

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prior art. (D.I. 201 at 21). I reject Defendants' attempt to use the opinion from a different case as factual evidence in this case.

composition of catalyst, and reaction time.[5] (*Id.*). Weiss discloses "pure" oxymorphone obtained by catalytic hydrogenation of 14-hydroxymorphinone. (Tr. 86:22-89:12; JTX-3 at 1507). It is undisputed, however, that Weiss does not quantify the amount of oxymorphone ABUK or other impurities remaining after hydrogenation. (Tr. 89:13-19, 542:21-543:1; *see also* JTX-3 at p. 1507). Weiss used a melting point analysis for determining the level of impurities present in the sample, a technique that was not capable of determining ABUK levels of ten ppm or lower. (Tr. 204:14-206:13, 504:5-505:10, 506:1-22, 527:7-18; JTX-3 at p. 1507; PTX-30 at p. 396). Weiss also teaches that oxymorphone ABUK and oxycodone ABUK have significant reactivity differences. (Tr. 550:15-552:18; JTX-3 at p. 1506). Between the publication of Weiss in 1957 and the date of invention in 2005, no other prior art reference mentioned hydrogenation of oxymorphone ABUK. (Tr. 527:19-24).

iv. Chapman

The parties dispute whether the Chapman reference is prior art. The Chapman reference is a United States patent application filed on March 30, 2005. (DTX-9 at cover). Chapman claims the benefit of the filing date of a provisional application filed on March 30, 2004. (*Id.*).

Defendants argue that Chapman qualifies as 35 U.S.C. § 102(e) prior art. That section provides that "an invention described in . . . an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent" is prior art. Since § 102(e) requires that the application predate "the invention," a patentee may "swear behind" a potential § 102(e) reference. Plaintiffs contend that under Defendants' obviousness theory, the claims of the '779 patent are entitled to a priority date of March 12,

[5] Defendants do not contest the fact that Weiss lacks these parameters. Defendants' expert, Dr. Gokel, opined that these were all "relatively standard" conditions and that a person of ordinary skill "could easily adjust the pH change to see if that was too acidic or not." (Tr. 89:20-90:18).

2004, when the inventors first produced low-ABUK oxycodone HCl. (D.I. 215 at 40). I am not persuaded by Plaintiffs' argument that a patent claim's priority date depends on the particular obviousness theory espoused by the patent's challenger. I have already determined that claims 1-6 of the '779 patent are entitled to a priority date of February 2, 2005. Since Chapman has a priority date of at least as early as March 30, 2004, Chapman qualifies as prior art.

Chapman does not discuss oxymorphone. Instead, Chapman describes a process for using hydrogenation to convert 14-hydroxycodeinone ("oxycodone ABUK") into oxycodone using a "double hydrogenation" process. (Tr. 92:3-21, 528:1-529:14). This process involves an initial step of hydrogenating oxycodone ABUK, resulting in oxycodone which still contains relatively high levels of oxycodone ABUK. (Tr. 529:1-4; DTX-9 at fig. 1, ¶ 13). Then, the oxycodone product from the first step is hydrogenated again under specific parameters, producing oxycodone with less than 25 ppm of oxycodone ABUK. (Tr. 529:5-14; DTX-9 ¶ 20).[6]

iv. Rapoport

The Rapoport reference is an article published in the Journal of the American Chemical Society in 1967. (DTX-421). Rapoport discloses the use of bisulfite addition to remove ABUK impurities. (Tr. 133:13-134:5; DTX-421 at p. 1942). Sulfur addition is a method that allows the ABUK impurities to be separated from the fully saturated compound by taking advantage of differences in solubility. (Tr. 134:12-135:9; DTX-421 at p. 1942). Once the solubility difference has been achieved, another method must be used to separate the saturated compound from its ABUK; Rapoport teaches the use of extraction to accomplish this. (Tr. 135:22-136:6).

Rapoport does not address the use of this method to separate ABUK impurities in

[6] Chapman also states that the process may reduce the levels of oxycodone ABUK to below 15 ppm, 10 ppm, or 5 ppm. (DTX-9 ¶ 16). In Example 3, Chapman stated that two different analytical methods showed levels of oxycodone ABUK at 5 ppm and 10 ppm. (Tr. 96:15-97:8; DTX-9 ¶¶ 197-98).

oxymorphone. (Tr. 531:11-14, 531:19-24). In fact, all of the examples discussed in Rapoport involve anisoles, such as oxycodone; unlike oxycodone, oxymorphone is not an anisole. (Tr. 531:4-10). Rapoport also does not report the precise level of impurities remaining at the end of the extraction, but indicates that the method is of limited effectiveness, as up to 25% of the ABUK impurities will remain after separation. (Tr. 141:6-11, 600:4-10; DTX-421 at p. 1945).

2. Comparing Prior Art and Claimed Subject Matter

Defendants first argue that it would have been obvious to a person of ordinary skill in the art to use catalytic hydrogenation to selectively hydrogenate the double bond in oxymorphone ABUK to form saturated oxymorphone. (D.I. 201 at 22). Defendants' expert, Dr. Gokel, opined that a catalytic hydrogenation reaction, like the type of reaction disclosed in Weiss, would result in reduction of ABUK impurities in oxymorphone to extremely low levels if driven to completion. (*Id.*; Tr. 82:3-84:3; DTX-164 at p. 607).

Dr. Gokel further opined that Chapman confirmed that catalytic hydrogenation could result in ABUK levels less than five ppm. (D.I. 201 at 23; Tr. 92:13-97:16; DTX-9 at ¶¶16, 22, 191-98). According to Defendants, a critical aspect of the Chapman reference was the identification of the reappearing ABUK problem, wherein diols, byproducts of the opioid synthesis, dehydrate in the presence of acid to form additional ABUK. (D.I. 201 at 23; Tr. 99:3-100:12; DTX-9 at ¶13, Fig. 2). According to Dr. Gokel, since oxymorphone ABUK and its diol react in the same way as oxycodone ABUK and its diol, Chapman's solution to the reappearing ABUK problem, removing the diol by dehydrating it to ABUK at the outset of the reaction, could be applied to achieve low-ABUK oxymorphone. (Tr. 99:21-101:24; DTX-9 at ¶¶ 61, 62).[7]

Plaintiffs respond that while Weiss "discloses the general concept of hydrogenating

[7] Defendants also argue that Casner confirms the solution to the diol problem described in Chapman. (D.I. 201 at 25). As I have determined that Chapman is not prior art, I will not address this argument.

oxymorphone ABUK to form oxymorphone," it does not disclose several "key reaction conditions." (D.I. 215 at 21; Tr. 526:17-23; 527:19-24). Plaintiffs also point out that Weiss does not disclose the level of ABUK impurities in the final product. (D.I. 215 at 21; Tr. 527:7-18). Plaintiffs' expert, Dr. Davies, explained that a person of ordinary skill would have read Weiss to teach that oxymorphone ABUK is easily converted to its diol form and that the diol could be converted back into oxymorphone ABUK under the hydrogenation reaction conditions. (Tr. 561:4-562:1). Dr. Davies opined that a person of ordinary skill would have expected some conversion of oxymorphone diol to oxymorphone ABUK to occur in many of the reaction steps Defendants' expert, Dr. Gokel, proposed for producing low-ABUK oxymorphone under the teachings of Weiss. (Tr. 563:8-564:3).

Plaintiffs also argue that Chapman does not render low-ABUK oxymorphone obvious because it is directed to a different compound, oxycodone and its ABUK, and discloses a different process, double hydrogenation, not the single hydrogenation of Weiss. (D.I. 215 at 22; DTX-9 at Fig. 1, ¶¶ 13, 20; Tr. 528:1-529:14). As to Defendants' assertion that Chapman "solved" the reappearing ABUK problem, Dr. Davies opined that Chapman did not disclose how to completely remove diol from oxycodone. (Tr. 567:24-568:6). In fact, Dr. Davies explained that Chapman's experiment resulted in 400 ppm of oxycodone diol remaining after the second hydrogenation step ran for almost twenty-two hours. (Tr. 567:2-23; DTX-9 at ¶ 192). According to Dr. Davies, therefore, a person of ordinary skill would not view Chapman as teaching how to remove diols or to produce low-ABUK oxycodone. (Tr. 567:2-568:6).

I find Dr. Davies testimony credible and more convincing than Dr. Gokel's testimony. It seems to me that even if a person of ordinary skill would view the oxycodone art as informative in researching possible solutions to reducing ABUK levels in oxymorphone, he would not find a

definitive solution in Chapman. Much of Dr. Gokel's testimony was hypothetical and, it seems to me, was colored by impermissible hindsight bias. His assertion that the reaction in Chapman could simply be run to completion in order to remove more diols is not credible in light of Dr. Davies' explanation of what would happen if the experiment were allowed to run for an extended period of time. Dr. Davies explained that the longer the experiment runs, "the slower the reaction to remove the last bit of the material is going to be." (Tr. 570: 18-21). Running the experiment for longer allows for side reactions to compete with the primary reaction and then "you'll start to hydrogenate other parts of the molecule and introduce other material." (Tr. 571:1-2). According to Dr. Davies, "If you run it forever, then you'll have – you won't have any product you want left at all." (Tr. 571:2-4). I find Dr. Davies explanation credible and believe that a person of ordinary skill in the art would have understood that it would not be feasible to simply run the reaction to completion as Dr. Gokel suggested.

Defendants' second argument is that a person of ordinary skill would have known to try sulfur addition and separation as a method of producing low-ABUK oxymorphone. (D.I. 201 at 27). Dr. Gokel explained that Rapoport taught that this method could be used to separate hydrocodone from its ABUK. (Tr. 133:13-136:23; DTX-421 at p. 1942). Dr. Gokel opined that a person of ordinary skill could have combined Rapoport's bisulfite separation method with either extraction, precipitation, or chromatography, all of which were well-known in the art, to achieve separation. (Tr. 145:21-146:19). Defendants contend that the viability of this method for producing low-ABUK oxymorphone was confirmed in 2014 when Johnson Matthey's subsidiary MacFarlan Smith used bisulfite addition to produce oxycodone with zero ppm ABUK impurity. (D.I. 201 at 27).[8]

[8] Defendants assert that a finding of fact from the European Opposition Division should be admissible to show "how a POSA views a piece of prior art." (D.I. 201 at 28 n.26). I disagree. As discussed at trial,

Plaintiffs respond that all of the examples disclosed in Rapoport involve anisole compounds, such as oxycodone. (D.I. 215 at 33-34; Tr. 598:4-5). Oxymorphone is a phenol, not an anisole. (Tr. 550:21-551:12). Plaintiffs further argue that Rapoport does not provide purity levels and there is no evidence that Rapoport, or anyone since, used this method to achieve ABUK levels below ten or five ppm. (D.I. 215 at 34; Tr. 598:8-9, 605:1-5). Plaintiffs contend that Rapoport teaches away from using the bisulfite addition method because it discloses that "approximately 25% of the ABUK will partition with the saturated ketone." (D.I. 215 at 34; Tr. 599:23-600:10). Dr. Davies testified that this was "not a very good partition ratio." (Tr. 600:9-10). Plaintiffs note that Defendants did not provide a single example where bisulfite extraction was used to achieve ABUK levels in any compound below ten ppm. (D.I. 215 at 34).

Plaintiffs also argue that a person of ordinary skill would not reasonably have expected that combining bisulfite addition with extraction, precipitation, or chromatography would produce low-ABUK oxymorphone. (D.I. 215 at 34). Rapoport only discloses bisulfite addition combined with extraction. (Tr. 598:6-7). According to Plaintiffs, Defendants have not provided any "detail about why a POSA would have been motivated to combine Rapoport with these other technologies and how, or indeed if, the combination . . . would work in practice." (D.I. 215 at 34-35).

I agree with Plaintiffs. As an initial matter, I do not think Rapoport teaches that low-ABUK oxymorphone can be achieved through bisulfite addition combined with extraction. It seems to me that the poor partition ratio, combined with the lack of any examples of this method being used successfully, would not inform a person of ordinary skill that this was a promising

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the fact-finding body in question operates under a different standard of proof than the clear and convincing standard that applies here. (Tr. 155:22-156:8). I declined to admit this document into evidence at trial and my opinion on its relevance has not changed. (Tr. 156:11-19).

method. Furthermore, I find Dr. Gokel's suggestion that it would have been obvious to a person of ordinary skill to combine Rapoport with precipitation or chromatography to be purely hypothetical. There is no evidence that anyone ever combined these methods prior to the invention date and Dr. Gokel himself never did any experiments to show that they would work; he merely opined that a person of ordinary skill would have thought to try it and would have expected it to work. Given the substantial evidence Plaintiffs presented that Rapoport disclosed such a poor partition profile, coupled with Dr. Davies' testimony that a person of ordinary skill would not have thought to combine Rapoport with precipitation or chromatography, it seems to me that Dr. Gokel's suggestion lacks credibility.

Defendants' only evidence that the technique purportedly worked is the experiment performed by Macfarlan Smith. This experiment, however, was performed on oxycodone, not oxymorphone, and Dr. Davies testified that there was no evidence that the experiment achieved ABUK reduction below ten ppm, as the instrumentation used to make the measurements was not disclosed. (Tr. 663:22-666:11). Furthermore, there is no evidence of record that shows the details of how this experiment was performed, i.e., whether the experimenter coupled bisulfite addition with precipitation, for example. (Tr. 667:23-668:5). I do not think this single experiment on a different compound indicates that Dr. Gokel's hypothetical processes would have been obvious to a person of ordinary skill in the art.

Defendants' third argument is that a person of ordinary skill in the art would have known that oxycodone could be converted to oxymorphone using O-demethylation, a process that was known in the prior art. (D.I. 201 at 29; Tr. 159:8-13). Since low-ABUK oxycodone was in the prior art, Defendants contend that a person of ordinary skill in the art would have known to use O-demethylation to convert low-ABUK oxycodone into low-ABUK oxymorphone. (D.I. 201 at

29). Defendants further contend that Mallinckrodt successfully used this process to produce oxymorphone having only six ppm of oxymorphone ABUK. (*Id.* at 30; Tr. 262:6-265:18).

Plaintiffs respond that the Mallinckrodt experiments are not confirmation of low-ABUK oxymorphone for at least two reasons. First, Plaintiffs note that Defendants rely on prior art oxycodone references in which the low-ABUK oxycodone was made using hydrogenation. (D.I. 215 at 36). The low-ABUK oxycodone used in the Mallinckrodt experiment, on the other hand, "was produced using Mallinckrodt's proprietary sulfur chemistry and therefore was not in the prior art." (*Id.*). Plaintiffs contend that the different processes result in different impurities and, therefore, the impurity profile of the starting material was not representative of the impurity profile of the prior art oxycodone on which Defendants rely. (*Id.* at 37).

I agree with Plaintiffs that the starting material matters in evaluating whether a person of ordinary skill would have found low-ABUK oxymorphone obvious because O-demethylation was available as a known method for converting oxycodone into oxymorphone. The person of ordinary skill at the time of invention would not have had access to the low-ABUK oxycodone Mallinckrodt used. As Plaintiffs point out, the prior art low-ABUK oxycodone had a different impurity profile that would result in differences in the final product of an O-demethylation reaction. Therefore, Mallinckrodt's experiment is not relevant to the obviousness analysis. This is significant because of the high quantities of diol present in the prior art low-ABUK oxycodone products that would be converted to ABUK during the O-demethylation process, resulting in more than ten ppm of oxymorphone ABUK in the final product. (Tr. 591:3-593:23).

Defendants' argument that a person of ordinary skill would have been able to eliminate the diol ABUK precursors at the outset to prevent this problem fails in light of the fact that there were no teachings in the prior art about how to eliminate diols. (D.I. 201 at 30; D.I. 215 at 38;

Tr. 567:10-14). It seems to me that Defendants' argument trivializes the many obstacles faced by the inventors in attempting to produce low-ABUK oxymorphone, is purely hypothetical in nature, and is also tinged with impermissible hindsight bias.

As to expectation of success, Defendants first argue that they need not prove reasonable expectation of success to prevail on their obviousness argument. (D.I. 201 at 31). Defendants further argue that reasonable expectation of success is probative of motivation. (*Id.*). I disagree on both points. The Federal Circuit has made clear that motivation to combine references and reasonable expectation of success are separate and distinct elements of the obviousness analysis: "one must have a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

Defendants cite to a single Federal Circuit case as support for their assertion that the FDA mandate can serve as motivation.[9] (D.I. 201 at 21 n.23). It is true "that FDA approval may be relevant to the obviousness inquiry." *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). As defendants note, the Federal Circuit has stated that, "The potential for FDA approval also may properly be considered . . . in determining whether one of ordinary skill would be motivated to develop a drug product and whether there was skepticism regarding the efficacy

[9] Defendants also cite to a district court opinion from the Southern District of New York in support of their argument. (D.I. 201 at 21 n.23). Not only is this decision not binding precedent, Defendants overstate the court's findings. The court did not find only that the industry "had a reason to develop low-ABUK oxycodone" because of the possibility of regulatory action. *In re OxyContin Antitrust Litig.*, 994 F. Supp. 2d 367, 404 (S.D.N.Y. 2014), aff'd sub nom. Purdue Pharma L.P. v. Epic Pharma, LLC, 811 F.3d 1345 (Fed. Cir. 2016). The court did not state that this was anything more than generalized motivation or identification of a problem to be solved and did not purport to hold that the FDA communications in that case constituted prior art. *Id.* Nor did the court reference the FDA communications in its discussion of whether a person of ordinary skill would have been motivated to combine prior art references. *Id.* at 405-06. I find this case to be neither persuasive nor relevant to Defendants' argument.

of such a product." *Id.* at 1291-92. Defendant misconstrues the meaning of this statement by taking it out of context, however. The court was not referring to a directive from the FDA as a source of motivation. In *Allergan*, the court found that a prior art reference provided motivation to formulate a combination product composed of two commercially available drugs, "in order to increase patient compliance." *Id.* at 1291. The court found error with the trial court's conclusion that a person of ordinary skill would not have been motivated to pursue the particular drug combination at issue "because the FDA did not consider improving patient compliance as a factor in its approval decision." *Id.* (quoting *Allergan, Inc. v. Sandoz Inc.*, 818 F.Supp.2d 974, 1016 (E.D.Tex.2011)). The court concluded, "Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Id.* at 1292. In other words, the motivation in *Allergan* came from a prior art reference, not from the FDA.

Since the FDA mandate was nothing more than a directive and provided no substantive teachings on how to produce low-ABUK oxymorphone, it cannot serve as a "motivation to combine" in an obviousness analysis. The FDA mandate may have provided motivation for pharmaceutical companies to pursue this invention, but that could only be relevant in the context of the prior art. "[K]nowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008). The FDA mandate provides nothing more than knowledge of the low-ABUK problem and motivation to solve it. It provides nothing substantive in the way of motivation to combine any prior art reference relevant to solving the problem.

Defendants also argue that the FDA mandate, coupled with the prior art references they presented at trial, together would have provided a person of ordinary skill with a reasonable

expectation of success. (D.I. 201 at 31-32). Defendants assert that "[t]he FDA does not issue unachievable directives." (*Id.* at 32). Defendants further argue that the fact that no one in the industry "protested the FDA's mandate" also demonstrates a reasonable expectation of success. (*Id.* at 34; Tr. 272:15-274:6).

I also do not think the FDA mandate provided a person of ordinary skill in the art with a reasonable expectation of success. Again, the communications from the FDA to the pharmaceutical companies were in the form of directives. These communications were not teachings and provided no substantive information about how the companies were to go about producing low-ABUK oxymorphone. In fact, the communications reveal that the FDA recognized the challenge the mandate posed for the companies. Simply because the companies did not protest the mandate does not, as Defendants argue, demonstrate a reasonable expectation of success. (D.I. 201 at 34).

3. Secondary Considerations

"[S]econdary considerations, when present, must be considered in determining obviousness." *Ruiz*, 234 F.3d at 667; *see also Cyclobenzaprine*, 676 F.3d at 1076 ("[E]vidence on these secondary considerations is to be taken into account *always*, not just when the decisionmaker remains in doubt after reviewing the art." (quoting *Cable Elec. Prods. v. Genmark, Inc.*, 770 F.2d 1015, 1026 (Fed. Cir. 1985))). Here, Plaintiff did not present any evidence on any secondary considerations. Defendants, however, argue that there is evidence of near-simultaneous invention by others in the industry. (D.I. 201 at 34). "Independently made, simultaneous inventions, made 'within a comparatively short space of time,' are persuasive evidence that the claimed apparatus 'was the product only of ordinary mechanical or engineering skill.'" *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir.

2010) (quoting *Concrete Appliances Co. v. Gomery*, 269 U.S. 177, 184 (1925)).

Defendants argue that the Dung patent confirms that catalytic hydrogenation works to achieve low-ABUK oxymorphone. (D.I. 201 at 25). Defendants agree that Dung is not prior art. (Tr. 696:5-6). Rather, Defendants argue that "[t]he Dung patent is evidence of near-simultaneous invention." (*Id.* at 26). Dung's priority date, December 14, 2006, post-dates the invention date of the '779 patent by almost two years. (DTX-16 at cover). Defendants argue that the invention claimed in the Dung patent was conceived of in January, 2006, or a little less than a year after the invention date of the '779 patent. (D.I. 219 at 17).

I do not think it matters whether the Dung patent is entitled to the earlier invention date. I do not think there was simultaneous invention under either invention date. It is true that the Federal Circuit has found simultaneous invention where the invention dates were separated by only about a year. *Geo. M. Martin Co.*, 618 F.3d at 1305. In that case, however, there was additional evidence of simultaneous invention by two other inventors, three and five years prior to the claimed invention's date of invention. *Id.* at 1305-06. As the Federal Circuit has cautioned, whether near simultaneous invention is an indication of obviousness must be considered in light of all of the circumstances. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1460 (Fed. Cir. 1984). Here, it is clear that a number of different pharmaceutical companies were attempting to produce low-ABUK oxymorphone in order to comply with the FDA mandate. I do not think that the fact that one other company was successful in doing so either one or two years after Plaintiffs is persuasive evidence of "near simultaneous" invention. I find that there was no simultaneous invention of any of claims 1-6 of the '779 patent.

For the reasons given above, I find that Defendants have not met their burden of proving

by clear and convincing evidence that any of claims 1-6 of the '779 patent are obvious.

IV. ANTICIPATION

Defendants' sole anticipation argument is predicated on adoption of their proposed claim construction; if I adopt Plaintiffs' proposed construction, there can be no anticipation under Defendants' theory.[10] The term in question is "14-hydroxymorphinone." Claim 1 is representative and reads as follows:

> 1. A hydrochloride salt of oxymorphone comprising less than 0.001% of *14-hydroxymorphinone*.

('779 patent, claim1) (disputed term italicized).

A. Legal Standard

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324) (alteration in original). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977–80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction

[10] At trial, Defendants presented a second anticipation argument based on Weiss's disclosure of "pure oxymorphone," which Defendants argued meant Weiss disclosed oxymorphone HCl with less than five parts per million of the ABUK impurity. (Tr. 42:2-21). Defendants failed to present this second argument in post-trial briefing. Therefore, this argument is deemed waived.

analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312–13 (citations and internal quotation marks omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314.

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a determination of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317–19 (internal quotation marks omitted). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per*

Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GMBH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (citation and internal quotation marks omitted).

B. Discussion

Defendants argue that this term should be construed to mean, simply, 14-hydroxymorphinone, the ABUK of the oxymorphone base. (D.I. 201 at 36). Plaintiffs contend that "14-hydroxymorphinone," properly construed in the context of the patent, would be understood by a person of ordinary skill in the art to mean "14-hydroxymorphinone hydrochloride," the HCl salt form of 14-hydroxymorphinone. (D.I. 215 at 45).

Defendants contend that the intrinsic evidence supports their reading of this claim term. (D.I. 201 at 36). Specifically, Defendants point to Reaction Scheme 4 ('779 patent, col. 9-10) and Example 3 ('779 patent at 37:16-39). (D.I. 201 at 36). Plaintiffs respond that Reaction Scheme 4 is "directed to 14-hydroxymorphinone within oxymorphone free base" and does nothing to inform the meaning of 14-hydroxymorphinone within the oxymorphone salt. (D.I. 215 at 46). As to Example 3, Plaintiffs note that Defendants' own expert, Dr. Gokel, admitted that a person of ordinary skill in the art would understand the reference to "14-hydroxymorphinone (14-OHM) impurity," read in the context of the patent, to mean the hydrochloride salt of 14-hydroxymorphinone. (*Id.*; '779 patent at 37:24-25; Tr. 200:16-201:16).

Plaintiffs argue that a person of ordinary skill in the art would understand that the ABUK impurity found in oxymorphone HCl necessarily must be itself in the HCl salt form. (D.I. 215 at 45). Plaintiffs further argue that because the patent is directed to oxymorphone with reduced ABUK impurity levels, and because the ABUK impurity only exists in the salt form, and not in the free base form, the term must be read to mean "14-hydroxymorphinone hydrochloride" to

avoid "absurd result[s]." (D.I. 215 at 46). Plaintiffs point out that the specification omits "HCl" when describing ABUK impurities. (*Id.*). Plaintiffs further point out that Defendants' own prior art references omit "HCl" when describing ABUK impurities in opioid HCl compounds. (*Id.*).

I agree with Plaintiffs that a person of ordinary skill would understand "14-hydroxymorphinone" as used in the claims of the '779 patent to mean the HCl salt form. It seems clear to me that both parties' experts, as well as other experts in the field, sometimes omit "HCl" or "hydrochloride" when referring to the hydrochloride salt form of ABUK impurities in opioid hydrochloride compounds. This is evident from the testimony of Defendants' own expert, Dr. Gokel, as to Example 3 of the '779 patent. (Tr. 200:16-201:16). This is also evident from contemporaneous references, including Chapman, Casner, and Dung. (DTX-9 at claim 1; DTX-8 at ¶36; DTX-16 at claim 1). Defendants have not cited to any evidence that rebuts the abundance of intrinsic and extrinsic evidence supporting Plaintiffs' proposed construction.

I will construe "14-hydroxymorphinone" to mean "14-hydroxymorphinone hydrocholoride." Defendants have made no argument that the asserted claims are anticipated under Plaintiffs' proposed construction. Therefore, since I adopt Plaintiffs' proposed construction, I need not address Defendants' asserted prior art. I hold that claims 1-6 of the '779 patent are not anticipated by the prior art.

V. WRITTEN DESCRIPTION

The written description requirement contained in 35 U.S.C. § 112, ¶ 1 requires that the specification "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharm., Inc., v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the

inventor had possession of the claimed subject matter as of the filing date." *Id.* "A party must prove invalidity for lack of written description by clear and convincing evidence." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015).

Defendants argue that the specification of the '779 patent does not have adequate written description support for the less than ten and less than five ppm limitations that were added during prosecution. (D.I. 201 at 39). Defendants contend that the only mention of impurity levels in oxymorphone in the specification is a single statement in Example 3 that "the sample contained no detectable amount of" the ABUK impurity. (*Id.*; '779 patent at 37:35-36). According to Defendants, this single statement, without any discussion of the detection limits of the experiment performed to measure impurities, is insufficient to show that the inventors possessed the low-ABUK oxymorphone claimed in the patent. (D.I. 201 at 40).

Plaintiffs respond by pointing to a portion of the specification they claim "clearly defines" the phrase "no detectable amount." (D.I. 215 at 48). The specification explains that the invention is directed to reducing the concentration of ABUK impurities, resulting in "a highly pure" oxymorphone product. ('779 patent at 27:25-30). The specification goes on to state that the product preferably comprises "less than about 0.001%," or ten ppm, or "may comprise less than about 0.0005%," or five ppm, of the ABUK impurity. (*Id.* at 27:42-7). The specification continues, "[s]till more preferably, no detectable amount of an [ABUK] compound is present in the" oxymorphone product. (*Id.* at 27:47-49). It seems clear to me that this disclosure indicates that "no detectable amount" is intended to mean at least less than five ppm in the context of the patent.

Plaintiffs also point to data reported in the specification obtained using the same mass spectrometry method used in Example 3, the oxymorphone example Defendants criticize for not

specifying a detection limit. (D.I. 215 at 48). As Plaintiffs note, using this same method, the inventors disclosed ABUK levels in oxycodone as low as 0.5 ppm. (*Id.*; '779 patent at 30:35-46). Defendants argue that this measurement of impurity levels in oxycodone is insufficient disclosure as to measurements of impurity levels in oxymorphone. (D.I. 201 at 40-41). I disagree. The specification discloses a measurement technique that is not unique to either oxymorphone or oxycodone. Plaintiffs' expert, Dr. Davies, testified that the instrument is "simply a counting device" and that any difference in the reactivity of the two molecules, which is relevant for eliminating the ABUK impurities, is not relevant for counting the molecules. (Tr. 637:3-638:13). I find Plaintiffs' expert credible. Even Defendants' expert, Dr. Gokel, testified that while the detection limits for the ABUKs of these two compounds were "not necessarily identical," a person of ordinary skill in the art would expect them to be similar. (Tr. 175:4-176:5).

I find that the disclosure of "no detectable amount" is sufficient to show that the inventors possessed oxymorphone with less than five ppm of 14-hydroxymorphinone. Therefore, Defendants have not proved by clear and convincing evidence that claims 1-6 of the '779 patent are invalid for lack of written description.

VI. CONCLUSION

Defendants failed to prove by clear and convincing evidence that claims 1-6 of the '779 patent are invalid.

Plaintiffs should submit an agreed upon form of final judgment within two weeks.[11]

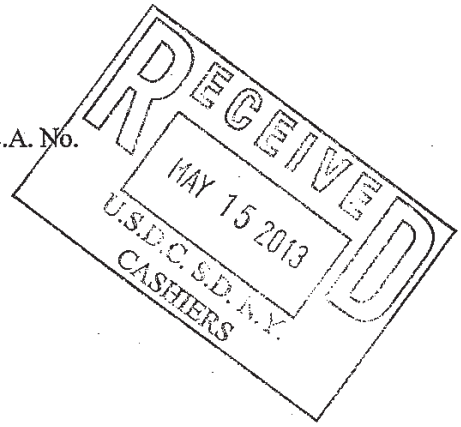
[11] Notwithstanding that Teva and some of the Actavis Defendants did not participate in the trial, they will still be bound by the final judgment. (D.I. 186 at 5:18-6:13; D.I. 175).

EXHIBIT L

13 CV 3284

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

ENDO PHARMACEUTICALS INC., Plaintiff, v. PAR PHARMACEUTICAL COMPANIES, INC. and PAR PHARMACEUTICAL, INC., Defendants.	C.A. No.



COMPLAINT

Plaintiff Endo Pharmaceuticals Inc. ("Endo") for its Complaint against Defendants Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc. (collectively "Par" or "Defendants"), allege as follows:

PARTIES

1. Plaintiff Endo is a Delaware corporation, having its principal place of business at 1400 Atwater Drive, Malvern, PA 19355. Endo is a specialty pharmaceuticals company engaged in the research, development, sale and marketing of prescription pharmaceuticals used, among other things, to treat and manage pain. Endo markets and distributes OPANA® ER CRF, an innovative tamper-resistant opioid.

2. Upon information and belief, Par Pharmaceutical Companies, Inc. is a corporation organized and existing under the laws of the State of Delaware, and its principal place of business is located at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677.

3. Upon information and belief, Par Pharmaceutical Companies, Inc. is a pharmaceutical company engaged in the research, development, manufacturing, marketing,

distribution, and sale of prescription pharmaceutical products throughout the United States, including in this judicial district.

4. Upon information and belief, Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware, and its principal place of business is located at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677.

5. Upon information and belief, Par Pharmaceutical, Inc. is a wholly-owned subsidiary of and serves as the generic drug division for Par Pharmaceutical Companies, Inc.

6. Upon information and belief, the acts of Par Pharmaceutical, Inc. complained of herein were done at the direction of, with the authorization of, and/or with the cooperation, participation, and assistance of, and at least in part for the benefit of, Par Pharmaceutical Companies, Inc.

NATURE OF ACTION

7. This is an action for arising under the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*. and the Declaratory Judgment Act, 28 U.S.C. § 2201, *et seq*.

JURISDICTION AND VENUE

8. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) (patent infringement), and 28 U.S.C. §§ 2201 and 2202 (declaratory judgment).

9. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and 1400(b).

10. This Court has personal jurisdiction over both of the Defendants by virtue of the fact that, *inter alia*, they have committed — or aided, abetted, planned, contributed to, or participated in the commission of — tortious conduct in the State of New York that has led to foreseeable harm and injury to Plaintiff.

11. Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc. are registered with the New York State Department of State as corporations actively conducting business within New York and maintain registered agents within the state.

12. Upon information and belief, Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc. collaborate in the research, development, manufacture, testing, distribution and/or the sale of a number of pharmaceutical products manufactured and sold pursuant to approved abbreviated new drug applications within the United States and the State of New York generally and this judicial district specifically.

13. Upon information and belief, Defendants conduct research & development, manufacturing, supply chain activities, account services, and distribution through one or more of their facilities, located in this judicial district. Furthermore, Par Pharmaceutical Companies, Inc. states on its website (http://www.parpharm.com/index.php?option=com content&view=article&id=72&Itemid=29) that it "[e]mploys more than 600 professionals in offices in Woodcliff Lake, New Jersey (Corporate Headquarters), Spring Valley, New York (Research & Development, Manufacturing, Supply Chain, and Account Services) and Suffern, New York (Distribution)."

14. Upon information and belief, Par intends to distribute and sell generic OPANA® ER in a non-tamper resistant form in this judicial district should ANDA No. 200792 be approved by FDA.

15. Moreover, Par maintains continuous and systematic contacts with the State of New York and this District.

16. Upon information and belief, Defendants currently sell significant quantities of generic drug products in New York. Those products include, inter alia, generic versions of

Ambien® CR and Wellbutrin® XL. Examples of other generic products manufactured and sold by Par are at http://www.parpharm.com/generics/index.php?option=comproducts&view=default&articleid=46&Itemid=79.

17. Upon information and belief, Par Pharmaceutical Companies, Inc. is registered with the New York State Department of State as a corporation actively conducting business within New York.

18. Upon information and belief, Par Pharmaceutical, Inc. is registered as a Pharmacy Establishment in the State of New York by the New York State Department of Education, Office of the Professions. (Registration Nos. 027015, 029055, and 101405.) The Registrations have an active status and are valid through November 30, 2013, July 31, 2014, and October 31, 2015, respectively.

19. Upon information and belief, Par plans to continue to maintain continuous and systematic contacts with the State of New York, including but not limited to, its aforementioned business of manufacturing, testing, distributing, and selling pharmaceuticals.

20. Furthermore, Par accepted that the U.S. District Court for the Southern District of New York has personal jurisdiction over it in *Endo Pharmaceuticals Inc., et al. v. Par Pharmaceutical Companies, Inc. et al.*, 12-cv-09261-TPG.

21. Based on the facts and causes alleged herein, and for additional reasons to be developed through discovery, this Court has personal jurisdiction over the Defendants.

FACTUAL BACKGROUND

Endo's OPANA® ER CRF NDA

22. On June 22, 2006, the United States Food and Drug Administration ("FDA") approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which contain

oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

23. On December 12, 2011, FDA approved Endo's Supplemental New Drug Application ("sNDA") 201655, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for OPANA® ER CRF.

24. OPANA® ER CRF is bioequivalent to the original OPANA® ER.

25. OPANA® ER CRF is a crush-resistant tablet that is intended to make the active ingredient, oxymorphone hydrochloride, more difficult to abuse. Endo discontinued sales of non-crush-resistant OPANA® ER (the "Discontinued Formulation") after FDA approved its sNDA for OPANA® ER CRF.

26. OPANA® ER CRF is distributed and sold throughout the United States for relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time.

ENDO'S PATENTS

27. On December 14, 2010, the PTO duly and legally issued U.S. Patent No. 7,851,482 ("the '482 Patent"), entitled "Method for Making Analgesics" to Johnson Matthey Public Limited Company ("Johnson Matthey") as assignee. Jen-Sen Dung, Erno M. Keskeny, and James J. Mencel are named as inventors. A true and correct copy of the '482 Patent is attached as Exhibit A.

28. Endo subsequently acquired full title to the '482 Patent, and accordingly, Endo is now the sole owner and assignee of the '482 Patent.

29. On November 13, 2012, the PTO duly and legally issued U.S. Patent No. 8,309,122 ("the '122 Patent"), entitled "Oxymorphone Controlled Release Formulations" to

Endo Pharmaceuticals, Inc. as assignee. Huai-Hung Kao, Anand R. Baichwal, Troy McCall, and David Lee are named as inventors. A true and correct copy of the '122 Patent is attached as Exhibit B.

30. Endo is the sole owner and assignee of the '122 Patent.

31. On December 11, 2012, the PTO duly and legally issued U.S. Patent No. 8,329,216 ("the '216 Patent"), entitled "Oxymorphone Controlled Release Formulations" to Endo Pharmaceuticals, Inc. as assignee. Huai-Hung Kao, Anand R. Baichwal, Troy McCall, and David Lee are named as inventors. A true and correct copy of the '216 Patent is attached as Exhibit C.

32. Endo is the sole owner and assignee of the '216 Patent.

33. Both OPANA® ER CRF and the original, now discontinued formulation of Opana ER are covered by one or more claims of each of the '482, '122, and '216 Patents.

34. Each of the '482, '122, and '216 Patents are listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") with reference to OPANA® ER CRF. Endo has also listed three additional patents licensed from Grünenthal GMBH, U.S. Patents 8,114,383, 8,192,722, and 8,309,060.

DEFENDANTS' INFRINGING PRODUCT

35. Before January 19, 2010, Watson Pharmaceuticals, Inc. ("Watson") filed Abbreviated New Drug Application ("ANDA") No. 200792 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacturing, use, and sale of generic oxymorphone hydrochloride extended release tablets ("Defendants' Generic Oxymorphone ER Tablets") as a generic version of the discontinued, non-crush-resistant formulation of OPANA® ER.

36. In response, Endo filed suit against Watson in the District of New Jersey alleging infringement of U.S. Patent No. 5,662,933 ("the '933 Patent") and U.S. Patent No. 5,958,456 ("the '456 Patent") by Defendants' Generic Oxymorphone ER Tablets. *See Endo Pharmaceuticals Inc., et al. v. Watson Pharmaceuticals, Inc.*, United States District Court, District of New Jersey, Dkt. No. 10-cv-1242 KSH-PS. Endo and Watson settled their infringement dispute in October, 2010. The case was dismissed by Order dated October 21, 2010. Nothing in the agreement granted Watson any license or other right to practice the inventions claimed in the '482, '122, or '216 Patents.

37. The '482, '122, and '216 Patents had not issued at the time Watson submitted its certification under § 505(j) of the Federal Food, Drug and Cosmetic Act.

38. Upon information and belief, in 2012 Watson sold ANDA No. 200792 to Par in accordance with a Consent Agreement with the United States Federal Trade Commission, described at http://www.ftc.gov/opa/2012/10/watson.shtm.

39. Upon information and belief, some time before November 8, 2012, Par submitted to FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of crush-resistant oxymorphone hydrochloride extended-release tablets as a generic version of the product described in sNDA 201655.

40. In a letter dated November 8, 2012, received by Endo on November 12, 2012, Par purported to notify Endo that Par had submitted ANDA No. 20-4340, naming Par Pharmaceutical, Inc. as the ANDA applicant and seeking approval to manufacture, use, or sell Par's ANDA Product before the expiration of the '482, '383, and '722 Patents. On November

16, 20120 Par sent Endo a letter that was substantially similar to the November 8, 2012 letter. The Par Notice Letters claimed that Par's ANDA included a Paragraph IV Certification stating that it was Par's opinion that the claims of the '482, '383, and '722 Patents are invalid, unenforceable, or are not infringed by the proposed manufacture, importation, use, sale, or offer for sale of the Par ANDA Products.

41. In response, Endo filed suit against Par in the Southern District of New York, alleging infringement of the '482, '383, and '722 Patents based on Par's filing of ANDA No. 20-4340. *See Endo Pharmaceuticals Inc. et al. v. Par Pharmaceutical Companies, Inc., et al.*, 12-cv-09261-UA. That Complaint also included three Counts asserting infringement of the '122, '216, and '060 Patents, which each issued after Par sent its Notice Letters to Endo.

42. Upon information and belief, Defendants plan to market and sell their Generic Oxymorphone ER Tablets described in ANDA No. 200792 as a generic substitute for OPANA® ER, and in competition with OPANA® ER CRF.

43. Defendants' marketing and sale of Defendants' Generic Oxymorphone ER Tablets will cause wholesale drug distributors, prescribing physicians and pharmacies to purchase, prescribe, and dispense in competition with and as a substitute for OPANA® ER CRF.

44. Defendants' manufacture and sale of Defendants' Generic Oxymorphone ER Tablets will cause Endo to suffer immediate and irreparable harm, including without limitation, irreparable injury to its business reputation and goodwill, lost sales of OPANA® ER CRF, the loss of the benefit of its investment in developing OPANA® ER and the reformulated crush-resistant version of OPANA® ER, and price erosion for OPANA® ER CRF.

COUNT I

(INFRINGEMENT OF THE '482 PATENT)

45. Endo incorporates each of paragraphs 1-44 above as if set forth fully herein.

46. Watson's submission of an ANDA and amendments thereto to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations of which it notified Endo on or about January 19, 2010, under which Par now seeks approval to market Defendants' Generic Oxymorphone ER Tablets prior to expiration of the '482 Patent, constitutes infringement under 35 U.S.C. § 271(e)(2)(A).

47. Defendants' commercial manufacture, offer for sale, or sale of Defendants' Generic Oxymorphone ER Tablets in the strengths set forth in its January 19, 2010 notice letter will infringe the '482 Patent under 35 U.S.C. § 271(a)-(c).

48. Upon information and belief, Defendants are aware of the existence of the '482 Patent, and are aware that the commercial manufacture, sale, and offer for sale of Defendants' Generic Oxymorphone ER Tablets will constitute infringement of the Patent.

COUNT II

(DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '482 PATENT)

49. Endo incorporates each of paragraphs 1-48 above as if set forth fully herein.

50. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

51. There is an actual case or controversy such that the Court may entertain Plaintiff's request for declaratory relief consistent with Article III of the United States Constitution, and this actual case or controversy requires a declaration of rights by this Court.

52. Defendants have made and will continue to make substantial preparation in the United States to manufacture, offer to sell, sell and/or import Defendants' Generic Oxymorphone ER Tablets before the expiration of the '482 Patent.

53. Defendants' actions, including, but not limited to, purchasing Watson's ANDA No. 200792, filing Par's ANDA No. 20-4340, and engaging in the 12-cv-9261-TPG patent litigation indicate their intention to manufacture, offer to sell, sell and/or import the products that

are the subject of that ANDA before the expiration of the '482 Patent, and further indicate a refusal to change the course of its action in the face of acts by Plaintiff.

54. Any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets before the expiration of the '482 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '482 Patent.

55. Plaintiff is entitled to a declaratory judgment that any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets by Defendants before the expiration of the '482 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '482 Patent.

COUNT III

(INFRINGEMENT OF THE '122 PATENT)

56. Endo incorporates each of paragraphs 1-55 above as if set forth fully herein.

57. Watson's submission of an ANDA and amendments thereto to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations of which it notified Endo on or about January 19, 2010, under which Par now seeks approval to market Defendants' Generic Oxymorphone ER Tablets prior to expiration of the '122 Patent, constitutes infringement under 35 U.S.C. § 271(e)(2)(A).

58. Defendants' commercial manufacture, offer for sale, or sale of Defendants' Generic Oxymorphone ER Tablets in the strengths set forth in its January 19, 2010 notice letter will infringe the '122 Patent under 35 U.S.C. § 271(a)-(c).

59. Upon information and belief, Defendants are aware of the existence of the '122 Patent, and are aware that the commercial manufacture, sale, and offer for sale of Defendants' Generic Oxymorphone ER Tablets will constitute infringement of the Patent.

COUNT IV

(DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '122 PATENT)

60. Endo incorporates each of paragraphs 1-59 above as if set forth fully herein.

61. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

62. There is an actual case or controversy such that the Court may entertain Plaintiff's request for declaratory relief consistent with Article III of the United States Constitution, and this actual case or controversy requires a declaration of rights by this Court.

63. Defendants have made and will continue to make substantial preparation in the United States to manufacture, offer to sell, sell and/or import Defendants' Generic Oxymorphone ER Tablets before the expiration of the '122 Patent.

64. Defendants' actions, including, but not limited to, purchasing Watson's ANDA No. 200792, filing Par's ANDA No. 20-4340, and engaging in the 12-cv-9261-TPG patent litigation indicate their intention to manufacture, offer to sell, sell and/or import the products that are the subject of that ANDA before the expiration of the '122 Patent, and further indicate a refusal to change the course of its action in the face of acts by Plaintiff.

65. Any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets before the expiration of the '122 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '122 Patent.

66. Plaintiff is entitled to a declaratory judgment that any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets by Defendants before the expiration of the '122 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '122 Patent.

COUNT V

(INFRINGEMENT OF THE '216 PATENT)

67. Endo incorporates each of paragraphs 1-66 above as if set forth fully herein.

68. Watson's submission of an ANDA and amendments thereto to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations of which it notified Endo on or about January 19, 2010, under which Par now seeks approval to market Defendants' Generic Oxymorphone ER Tablets prior to expiration of the '216 Patent, constitutes infringement under 35 U.S.C. § 271(e)(2)(A).

69. Defendants' commercial manufacture, offer for sale, or sale of Defendants' Generic Oxymorphone ER Tablets in the strengths set forth in its January 19, 2010 notice letter will infringe the '216 Patent under 35 U.S.C. § 271(a)-(c).

70. Upon information and belief, Defendants are aware of the '216 Patent, and are aware that the commercial manufacture, sale, and offer for sale of filing of Defendants' Generic Oxymorphone ER Tablets will constitute infringement of the Patent.

COUNT VI

(DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '216 PATENT)

71. Endo incorporates each of paragraphs 1-70 above as if set forth fully herein.

72. This claim arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

73. There is an actual case or controversy such that the Court may entertain Plaintiff's request for declaratory relief consistent with Article III of the United States Constitution, and this actual case or controversy requires a declaration of rights by this Court.

74. Defendants have made and will continue to make substantial preparation in the United States to manufacture, offer to sell, sell and/or import Defendants' Generic Oxymorphone ER Tablets before the expiration of the '216 Patent.

75. Defendants' actions, including, but not limited to, purchasing Watson's ANDA No. 200792, filing Par's ANDA No. 20-4340, and engaging in the 12-cv-9261-TPG patent litigation indicate their intention to manufacture, offer to sell, sell and/or import the products that are the subject of that ANDA before the expiration of the '216 Patent, and further indicate a refusal to change the course of its action in the face of acts by Plaintiff.

76. Any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets before the expiration of the '216 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '216 Patent.

77. Plaintiff is entitled to a declaratory judgment that any commercial manufacture, use, offer for sale, sale, and/or importation of Defendants' Generic Oxymorphone ER Tablets by Defendants before the expiration of the '216 Patent will constitute direct infringement, contributory infringement, and/or active inducement of infringement of the '216 Patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Endo respectfully requests the following relief:

A. A judgment that Defendants infringe the '482 Patent;

B. A declaration that Defendants' commercial manufacture, distribution, use and sale of Defendants' Generic Oxymorphone ER Tablets would infringe the '482 Patent;

C. A judgment that Defendants infringe the '122 Patent;

D. A declaration that Defendants' commercial manufacture, distribution, use and sale of Defendants' Generic Oxymorphone ER Tablets would infringe the '122 Patent;

E. A judgment that Defendants infringe the '216 Patent;

F. A declaration that Defendants' commercial manufacture, distribution, use and sale of Defendants' Generic Oxymorphone ER Tablets would infringe the '216 Patent;

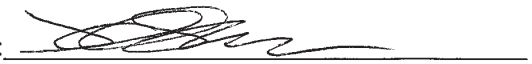
G. Preliminary and permanent injunctive relief restraining and enjoining Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '482, '122, and '216 Patents, for the full terms thereof, including any extensions;

H. A declaration that this an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

I. Reasonable attorneys' fees, filing fees, and reasonable costs of suit incurred by Endo in this action; and

J. Such other and further relief as the Court may deem just and proper.

Dated: May 15, 2013

By: 

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14919469

EXHIBIT A

US007851482B2

(12) **United States Patent**
Dung et al.

(10) **Patent No.: US 7,851,482 B2**
(45) **Date of Patent: Dec. 14, 2010**

(54) **METHOD FOR MAKING ANALGESICS**

(75) Inventors: **Jen-Sen Dung**, Boothwyn, PA (US); **Erno M. Keskeny**, Wilmington, DE (US); **James J. Mencel**, North Wales, PA (US)

(73) Assignee: **Johnson Matthey Public Limited Compnay**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 646 days.

(21) Appl. No.: **11/866,840**

(22) Filed: **Oct. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146601 A1 Jun. 19, 2008

(30) **Foreign Application Priority Data**

Dec. 14, 2006 (GB) 0624880.1

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/04 (2006.01)

(52) **U.S. Cl.** **514/282**; 546/45; 546/44

(58) **Field of Classification Search** 514/282; 546/45, 44

See application file for complete search history.

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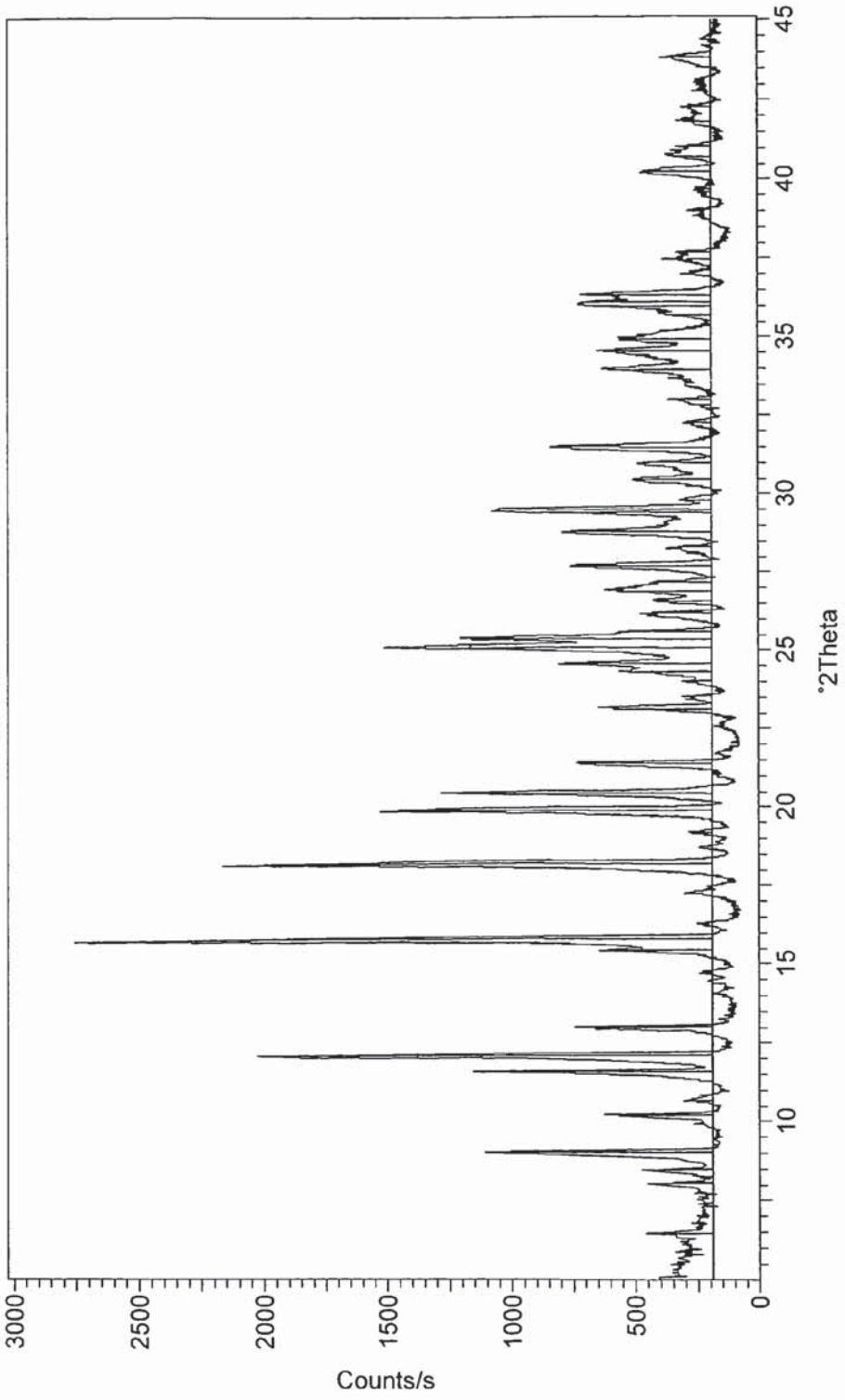
Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—RatnerPrestia

(57) **ABSTRACT**

Improved analgesic oxymorphone hydrochloride contains less than 10 ppm of alpha, beta unsaturated ketones and pharmaceutical preparations comprising such oxymorphone hydrochloride. The oxymorphone hydrochloride is produced by reducing a starting material oxymorphone hydrochloride using gaseous hydrogen and under specified acidity, solvent system and temperature conditions. A specific polymorph of oxymorphone hydrochloride may be obtained by hydration.

21 Claims, 1 Drawing Sheet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METHOD FOR MAKING ANALGESICS

FIELD OF THE INVENTION

This invention concerns an improved method for making analgesics, more especially for making the opiate oxymorphone as its hydrochloride.

BACKGROUND OF THE INVENTION

Oxymorphone, generally administered in the form of its hydrochloride salt, is a potent semi-synthetic opiate analgesic, for the relief of moderate to severe pain, and has been approved for use since 1959. It can be administered as an injectable solution, suppository, tablet or extended release tablet. It is desirable to develop high purity forms of oxymorphone and a method for its synthesis.

Several methods for synthesising oxymorphone from compounds isolated from the opium poppy or compounds derived therefrom are known, for example, starting from morphine, thebaine, or from oxycodone. There remains the need for methods which permit the formation of oxymorphone with low contamination of alpha, beta unsaturated ketones. The present invention provides an improved oxymorphone product and a method for producing such oxymorphone.

U.S. Pat. No. 7,129,248 claims a process for producing oxycodone hydrochloride with less than 25 ppm of 14-hydroxycodeinone, by hydrogenating oxycodone having greater than 100 ppm 14-hydroxycodeinone. The synthetic route to oxycodone taught in US'248 starts from thebaine and produces 14-hydroxycodeinone as an intermediate product and 8,14-dihydroxy-7,8-dihydrocodeinone as a by-product resulting from over-oxidation of thebaine. During conversion of oxycodone free base to the hydrogen chloride salt, the by-product may undergo acid-catalysed dehydration and be converted into 14-hydroxycodeinone. Thus the final oxycodone hydrogen chloride salt contains unreacted 14-hydroxycodeinone as well as 14-hydroxycodeinone derived from the by-product 8,14-dihydroxy-7,8-dihydrocodeinone. A hydrogenation step is claimed to reduce contents of 14-hydroxycodeinone from at least 100 ppm to less than 25 ppm.

SUMMARY OF THE INVENTION

The present invention provides an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones.

The invention also provides a method of purifying oxymorphone hydrochloride to yield an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones, which method comprises reducing a starting material oxymorphone hydrochloride in a strongly acid water and alcohol solvent, using gaseous hydrogen at a temperature in the range from 60 to 70° C. Reduction is suitably carried out for a period of at least 20 hours, but in another embodiment, reduction is carried out for 1 to 20 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described below with reference to the drawing, in which:

FIG. **1** is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the solvent is ethanol/water, although other water miscible alcohols, such as isopropanol and n-propanol, may be used. The reaction medium is very acidic, preferably by incorporating at least two equivalents of hydrochloric acid. A pH of less than 1 is desirable.

The reaction temperature is most preferably maintained at about 65° C. Hydrogen is conveniently supplied to the reaction vessel at 2.41 bar pressure.

The method of the invention has been able to reduce starting material oxymorphone hydrochloride having very high (of the order of 0.3 to 0.5%, or 3,000 to 5,000 ppm) content of alpha, beta unsaturated ketones to less than 10 ppm, and in many cases to undetectable levels (by HPLC).

The starting material oxymorphone hydrochloride may be an isolated or non-isolated material. Desirably, it has been obtained by the formation of the hydrogen chloride salt by heating oxymorphone free base in the presence of hydrochloric acid and an alcohol/water reaction medium. Suitable temperatures are 60-70° C. It can be seen that the reaction medium is ideal for the reduction of the method of the invention, so that it is generally not necessary to isolate the oxymorphone hydrochloride. However, the starting material oxymorphone hydrochloride may be isolated from the reaction medium or may be from another source.

The oxymorphone free base is itself preferably prepared by a reduction of 14-hydroxymorphinone. This may be carried out in a single- or two-stage process. The reduction is preferably carried out in acetic acid using gaseous hydrogen and a palladium on carbon catalyst. Preferred temperatures are of the order of 30° C. The base is precipitated by adding aqueous ammonia (NH_4OH).

This reduction may be in the presence of the reaction medium to which is added dichloromethane in methanol, Florasil and n-propanol.

The 14-hydroxymorphinone itself is most suitably prepared by hydroxylation of oripavine, using hydrogen peroxide in the presence of formic acid.

Oripavine is a known compound, which is extractable from poppy straw. The strain developed in Tasmania to be a high-Thebaine-yielding strain also produces higher than normal levels of oripavine.

The process of the invention is highly flexible, permitting many reaction steps to be carried out without isolation of intermediate products, whilst still retaining high (of the order of 50%) overall yields from oripavine, as well as remarkably high purity. Under favourable conditions, the presence of alpha, beta unsaturated ketones is undetectable by conventional means such as HPLC, but the skilled person can readily achieve less than 10 ppm contamination. The process of the invention has been successfully carried out at kilogram scale.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active component. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, colouring, flavouring and/or aro-

matic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, solutions, suspensions, etc.

In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described herein.

When the dosage form is oral, the dosage form of the present invention contains from about 1 mg to about 40 mg of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Particularly preferred dosages are about 5 mg, about 10 mg, about 20 mg or about 40 mg however other dosages may be used as well. The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release of having less than 10 ppm of alpha, beta unsaturated ketones. Such formulations can be prepared in accordance with US 2003/129230 A1, US 2003/129234 A1 and US 2003/157167 A1.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material that is incorporated into a matrix along with the oxymorphone salt thereof.

The sustained release dosage form may optionally comprise particles containing oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, and a plurality of the resultant solid sustained release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The sustained release bead formulations of the present invention slowly release the active component of the present

invention, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticiser is added to the hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with the agent(s) of the present are prepared, e.g., by dissolving the agent(s) in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active to the beads, and/or to color the solution, etc. For example, a product that includes hydroxypropylmethylcellulose, etc with or without colorant (e.g., Opadry™, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in these example beads, may then be optionally overcoated with a barrier agent, to separate the active component(s) from the hydrophobic sustained release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticiser, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticiser. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticiser, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Colour may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, colour may be added to Aquacoat™ via the use of alcohol or propylene glycol based colour dispersions, milled aluminium lakes and opacifiers such as titanium dioxide by adding colour with shear to water soluble polymer solution and then using low shear to the plasticised Aquacoat™. Alternatively, any suitable method of providing colour to the formulations of the present invention may be used. Suitable ingredients for providing colour to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and colour pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticised hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidised-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic

material, a further overcoat of a film-former, such as Opadry™, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the agent(s) from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents, which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semipermeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864.

Matrix Formulations

In other embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a sustained release coating as set forth herein. The materials suitable for inclusion in a sustained release matrix may depend on the method used to form the matrix.

For example, a matrix in addition to the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may include: hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. The list is not meant to be exclusive, any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit™. RSPO—the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° C. and 90° C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly (methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 25° C. to about 200° C., preferably from about 45° C. to about 90° C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For the purposes of the present invention, a wax-like substance is defined as any material that is normally solid at room temperature and has a melting point of from about 25° C. to about 100° C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° C. and 90° C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropyl-methylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxymorphone hydrochloride release required. The at least

one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioidoxycmorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a (w/w) of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

Matrix—Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} to C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxalkyl cellulose granules with water.

In yet other alternative embodiments, a spheronizing agent, together with the active component can be spheronized to form spheroids. Microcrystalline cellulose is a preferred spheronizing agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropyl-cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 mm to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 hours to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, the oxymorphone hydrochloride

having less than 10 ppm of alpha, beta unsaturated ketones, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For the purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 mm to about 12 mm in length and have a diameter of from about 0.1 mm to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tabletting equipment using standard techniques. Techniques and compositions for making tablets (compressed and moulded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681, described in additional detail above.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule containing the multiparticulates can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2% to about 30%, although the overcoat may be greater depending upon the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded particles before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release agent for prompt release. The immediate release agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., sustained release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of sustained release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the agent(s), e.g. when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the active in desired areas of the gastrointestinal (GI) tract, e.g. the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2% to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail U.S. Pat. No. 5,273,760, U.S. Pat. No. 5,286,493, U.S. Pat. No. 5,324,351, U.S. Pat. No. 5,356,467, and U.S. Pat. No. 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose,

although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described as fully polymerised copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings, which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™ from Rohm Tech, Inc. There are several different types of Eudragit™, for example Eudragit™ E is an example of a methacrylic acid copolymer that swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, or 10% Eudragit™ RL and 90% Eudragit™ RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticiser in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticiser into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticiser included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 wt % to about 50 wt % of the film-former. Concentration of the plasticiser, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

The addition of a small amount of talc may also help reduce the tendency of the aqueous dispersion to stick during processing, and may act as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be pumped, diffuse or migrate through a fibre, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be

formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. No. 4,200,098 and U.S. Pat. No. 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_nH_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethyl-cellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as an osmogel), whereby they push the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulphate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulphate, sodium sulphate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkyl-cellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a non-toxic colorant or dye. Examples of colourants or dyes include but are not limited to Food and Drug Administration Colourants (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation, semipermeable crosslinked polystyrenes, semipermeable crosslinked poly(sodium styrene sulfonate), semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride) and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present

invention are known in the art including those in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones equivalent to 10 to 40 mg oxymorphone hydrochloride, 25 mg to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 mg to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 mg to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Preparation of sustained release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the suppository base, or the melting of the base and subsequent partition of the drug from the suppository base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular suppository base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factors affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionisation, and lipid solubility.

The suppository base chosen should be compatible with the active of the present invention. Further, the suppository base is preferably non-toxic and non-irritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol™ (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20% to about 90% by weight of the total weight of the suppository. Preferably, the amount of suppository base in the suppository is from about 65% to about 80%, by weight of the total weight of the suppository.

Additional Embodiments

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may be used as a substitute for the oxymorphone hydrochloride in any existing commercial product such as, e.g., Opana™, Opana ER™ and Numorphan™. Such formulations are listed in the FDA Orange Book.

EXAMPLES

The invention will now be illustrated by the following examples, showing the synthesis of the high purity oxymorphone, starting from oripavine.

FIG. **1** is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

Example 1.1A

Hydroxylation of Oripavine to 14-hydroxymorphinone

1 kg oripavine is added with stirring to a reaction vessel containing 2.76 kg of formic acid and 0.53 kg water, and stirring is continued until the oripavine is completely dissolved, and the temperature remains in the range 20-30° C. Subsequently, 0.36 kg of 35 wt % hydrogen peroxide solution

is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction vessel is cooled to 10° C. and 7.12 litres of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 40° C. If necessary, the pH of the reaction mixture is adjusted to the range 8 to 10, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 3-5 hours.

A precipitate of product 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water until colourless and then dried to a damp cake and collected for the next stage.

Example 1.1B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with kg litre water and 0.73 kg acetic acid before adding 1 kg of 14-hydroxymorphinone prepared as in Example 1.1A and the mixture stirred until clear. 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen, and hydrogen supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, the pH of the filtrate is adjusted to pH 9 using ammonium hydroxide solution, the product precipitates and is isolated by filtration and dried under vacuum. The product is dissolved in dichloromethane/methanol (9:1 v/v) and slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 66% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.51% by area measurement.

Example 1.1C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 1 kg of oxymorphone base, prepared as in Example 1.1B, together with 2.05 kg of absolute alcohol and 0.66 kg of water. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 0.66 kg concentrated hydrochloric acid, 0.24 kg of water and 0.31 kg of absolute alcohol is added to the oxymorphone base slurry and the pH checked to ensure that it is <1.0. 40 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through Celite and a 0.2 μm polish filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is washed with absolute alcohol then dried. Yield is 80%.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 6.2 ppm.

Example 1.2A

Hydroxylation of Oripavine to 14-hydroxymorphinone

40 g of Oripavine is added with stirring to a reaction vessel containing 30 g of water and 85 g of formic acid, and stirring continued until oripavine is completely dissolved. The temperature remains in the range 20-30° C. Subsequently, 17.72 g of 30 wt % hydrogen peroxide solution is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction mixture is cooled to <20° C. and 335 mL of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 32° C. If necessary, the pH of the reaction mixture is adjusted to 9.0, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 2 hours at 20 C and 2 hours at 4-5° C.

A precipitate of 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water and then dried to a damp cake and collected for the next stage.

Example 1.2B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with 148 g of water, 90.6 g of acetic acid, and 250 g of damp 14-hydroxymorphinone (48% water content), prepared as in Example 1.2A. The mixture is stirred until clear then 1.34 g of 10% Pd on carbon catalyst (dry weight) in the form of a paste is added under a stream of nitrogen. The hydrogenation vessel is flushed with nitrogen and hydrogen respectively, and then the reaction mixture is hydrogenated at 30° C. and 35 psi (2.41 bar) for 5 hours. An in process test by HPLC indicates an 14-hydroxymorphinone area of 0.07%.

Once it is assessed that the reaction is complete, the catalyst is filtered off through a pad of celite, and the celite cake is washed with 25 mL water. The filtrate is cooled to 0-5° C. and the pH is adjusted to 9.5±0.5 with 1:1 mixture (V/V) of concentrated ammonium hydroxide and water. The precipitate is stirred at 0-5° C. for one hour and isolated by filtration. The crude product is dried in vacuum oven at 50° C. to afford 113 g (86.9% yield) of light beige solid. A sample of product is tested by HPLC for alpha, beta unsaturated ketone, and is found to contain 0.27% by area measurement.

113 g of crude oxymorphone base is taken up in 1.13 L of dichloromethane/methanol (9:1, v/v). 113 g of florisil is added to the solution and the mixture is stirred for 12 hours. The mixture is filtered through a pad of 113 g of florisil, and the florisil cake is rinsed with 120 mL of dichloromethane/methanol. The solvent is removed by distillation and then switched to n-propanol. The batch is cooled to 0-5° C. and stirred for 1 hour to precipitate the oxymorphone base, which is filtered off, washed with cold n-propanol, and dried in a vacuum oven to afford 67.2 g (59.47%) of white solids.

A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.027% by area measurement.

Example 1.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 50.1 g of oxymorphone base, prepared as in Example 1.2B, together with 120 g of absolute alcohol. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 32.7 g concentrated hydrochloric acid and 33.6 g of water is added to the oxymorphone base slurry and the pH is checked to ensure that it is <1.0. 2.0 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65° C. The reaction mixture is filtered whilst hot through Celite. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with absolute alcohol and then dried to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 1.1 ppm.

The above method may be varied by the skilled person whilst still maintaining excellent purity of the product oxymorphone hydrochloride, and examples of such variations follow.

Example 2.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 2.5 kg of water and 0.73 kg of acetic acid and 1 kg of 14-hydroxymorphinone is added to the vessel. The reaction mixture is stirred until a clear solution is obtained before 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, dichloromethane/methanol (9:1 v/v) is added to the filtrate and the mixture is adjusted to pH 9-10 by adding ammonium hydroxide solution. The dichloromethane/methanol phase is separate, slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 73% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 35 g of water, 17 g of acetic acid and 38.08 g of 14-hydroxymorphinone, prepared in Example 1.2A. The reaction mixture is stirred until a clear solution is obtained before 1.8 g of wet 5% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 4 hours. The reaction vessel is cooled to less than 25° C., and a sample is analyzed by HPLC to check for 14-hydroxymorphinone. The 14-hydroxymorphinone area detected by HPLC is 0.26%.

Once it is assessed that the reaction is complete, the catalyst is filtered off and the cake is washed with 15 mL of water. 180 mL of dichloromethane/methanol (9:1, v/v) are added to the filtrate and the pH of the mixture is adjusted to pH 9-10 by adding concentrated ammonium hydroxide. The dichloromethane/methanol layer is separated and purified by slurrying with ca. 20 g florisil. The slurry is filtered and the filtrate is distilled to exchange into n-propanol, and the mixture is cooled to 0-5° C. and stirred for 1-2 hours to precipitate oxymorphone base, which is isolated by filtration. The oxymorphone base is then slurried from n-propanol providing product in 74% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 2.5 g of oxymorphone base, prepared as in Example 2.2B, together with 7.5 mL of absolute alcohol, 2.5 g of water and 1.66 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.111 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 21 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with cold absolute alcohol and dried under vacuum to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 2.8 ppm.

Example 3.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Hydrochloride

The procedure for forming the oxymorphinone free base is followed as shown above, but instead of isolating the free base from a dichloromethane/methanol solution, 0.35 volume equivalents of 3N hydrochloric acid are added (vs the volume of the dichloromethane/methanol solution), the reaction mixture is stirred, allowed to stand, and the aqueous layer (contains the product) is separated from the organic layer. The aqueous layer is distilled under vacuum to remove ca. 50% of the volume, and then the remaining solution is cooled over 2 hour to 20-25° C., stirred for 1-2 hours, cooled to 0-5° C. and stirred 2-3 hours. The white solids that form during stirring are filtered off and washed with cold isopropanol. The yield is 64% and the product contains 0.34% of alpha, beta unsaturated ketones.

Example 3.1C

Purification of Oxymorphone Hydrochloride

Using an analogous process to Example 1.1C, but starting from the product of Example 3.1B, purified oxymorphone hydrochloride is obtained in a yield of 92% and having an undetectable content of alpha, beta unsaturated ketones.

Example 3.2C

Preparation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 5.05 g of oxymorphone hydrochloride, prepared in Example 3.1B, together with 13.5 mL of absolute alcohol, 4.5 mL of water and 1.51 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.21 g of 10% Pd on charcoal catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form a precipitate. The precipitate is collected by filtration, washed with cold absolute alcohol then dried. Yield is 92%.

A sample of the product is tested by HPLC and found to have an undetectable content of alpha, beta unsaturated ketones.

Without changing the basic process steps, but with small variations in the process steps for starting materials, such as isolation or not of such starting materials, and utilising the essential reduction requirements of the invention for the final step to the purified oxymorphone hydrochloride, other products have been obtained with levels of alpha, beta unsaturated ketones of 3.8 ppm, 1.7 ppm, 6.2 ppm, 6.9 ppm, 2.8 ppm, 3.1 ppm, 0.9 ppm, 6.0 ppm and another undetectable, or zero.

Example 3.2D

Hydration of Oxymorphone Hydrochloride

A drying dish is charged with oxymorphone hydrochloride, prepared as in Example 1.1C, 1.2C, 2.2C, 3.1C or 3.2C, which contains about 5-13 wt % of ethanol. The sample is placed in a vacuum oven along with a dish containing 100 mL of water. A vacuum is applied at 24-29 in Hg and the oven maintained at 20-40° C. for 24 hours. An ethanol-free or low ethanol (approx. 0.04 wt %) product is afforded containing about 10-13 wt % of water. The water absorbed by the sample may be removed in a vacuum oven at 50-55° C. The drying process is stopped when the product's KF is 6-8 wt %. The final hydrated oxymorphone hydrochloride affords a uniform polymorph with a consistent X-ray diffraction pattern.

What is claimed:

1. Oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone.

2. Oxymorphone hydrochloride according to claim **1**, wherein the content of 14-hydroxymorphinone is less than 5 ppm.

3. A pharmaceutical formulation comprising at least one pharmaceutically acceptable excipient and the oxymorphone hydrochloride according to claim **1**.

4. A method of treating pain comprising administering a pharmaceutical formulation according to claim **3** to a patient in need thereof.

5. A method of purifying a starting material of either oxymorphone or oxymorphone hydrochloride to yield the oxymorphone hydrochloride according to claim **1**, comprising exposing the starting material oxymorphone or oxymorphone hydrochloride to hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C. for a time sufficient to provide the less than 10 ppm of 14-hydroxymorphinone.

6. The method according to claim **5**, wherein the exposing is carried out for a period of at least 20 hours.

7. The method according to claim **5**, wherein the reaction medium has a pH of less than 1.

8. The method according to claim **5**, wherein the acid is hydrochloric acid.

9. The method according to claim **5**, wherein the temperature is approximately 65° C.

10. The method according to claim **5**, wherein the starting material oxymorphone or oxymorphone hydrochloride has not been isolated from a reaction mixture in which it is formed.

11. The method according to claim **5**, wherein the starting material oxymorphone or oxymorphone hydrochloride has been prepared by a process comprising reduction of 14-hydroxymorphinone.

12. The method according to claim **11**, wherein the 14-hydroxymorphinone that is reduced is prepared by a process of hydroxylating oripavine.

13. The method according to claim **12**, wherein the oripavine is derived from concentrated poppy straw.

14. The method according to claim **13**, wherein the concentrated poppy straw is derived from a high-Thebaine-yielding strain of poppy.

15. The method according to claim **5**, comprising the additional steps of subsequently forming crystalline oxymorphone hydrochloride and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the crystalline oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

16. The method according to claim **15**, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by exposure to reduced pressure.

17. The method according to claim **15**, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by heating the oxymorphone hydrochloride to a temperature in the range of from 50 to 55° C. under reduced pressure.

18. A method of making hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and a KF of 6-8 wt %, comprising exposing a starting material of oxymorphone or oxymorphone hydrochloride to gaseous hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C., subsequently forming crystalline oxymorphone hydrochloride, and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

19. Hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and having peaks within the following 20 ranges when analyzed by Powder X-Ray Diffraction: 8.5-9.5, 11.0-12.0, 11.5-12.5, 12.4-13.4, 15.2-16.2, 17.6-18.6, 19.3-20.3, 19.9-20.9, 24.6-25.6, 24.9-25.9, 29.0-30.0 and 31.0-32.0.

20. Oxymorphone hydrochloride prepared by the method of claim **5**.

21. Hydrated oxymorphone hydrochloride prepared by the method of claim **18**.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

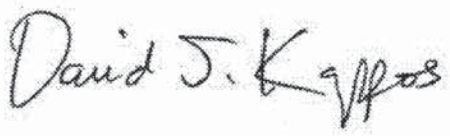
CERTIFICATE OF CORRECTION

PATENT NO.	: 7,851,482 B2
APPLICATION NO.	: 11/866840
DATED	: December 14, 2010
INVENTOR(S)	: Jen-Sen Dung et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 23, line 3, delete "20 ranges" and insert therefor --2Θ ranges--.

Signed and Sealed this
Nineteenth Day of July, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT B

US008309122B2

(12) United States Patent
Kao et al.

(10) Patent No.: US 8,309,122 B2
(45) Date of Patent: *Nov. 13, 2012

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1344 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/680,432**

(22) Filed: **Feb. 28, 2007**

(65) **Prior Publication Data**

US 2007/0134328 A1 Jun. 14, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on Jul. 3, 2002.

(60) Provisional application No. 60/303,357, filed on Jul. 6, 2001, provisional application No. 60/329,432, filed on Oct. 15, 2001, provisional application No. 60/329,444, filed on Oct. 15, 2001, provisional application No. 60/329,445, filed on Oct. 15, 2001.

(51) **Int. Cl.**

A61K 9/22	(2006.01)
A61K 9/34	(2006.01)
A61K 9/36	(2006.01)

(52) **U.S. Cl.** **424/464**; 424/468; 424/470; 424/479; 424/481; 424/482; 424/486

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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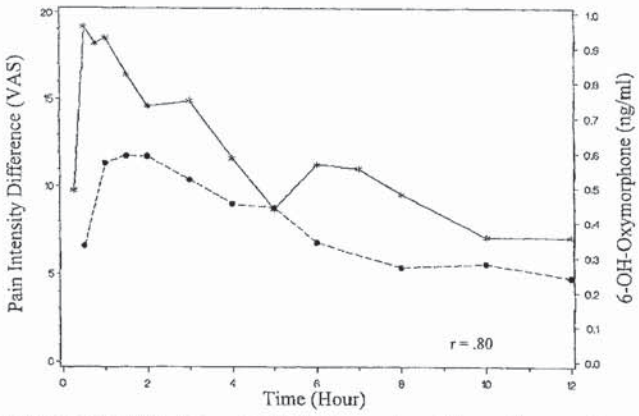
(74) *Attorney, Agent, or Firm* — Mayer Brown LLP

(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

20 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

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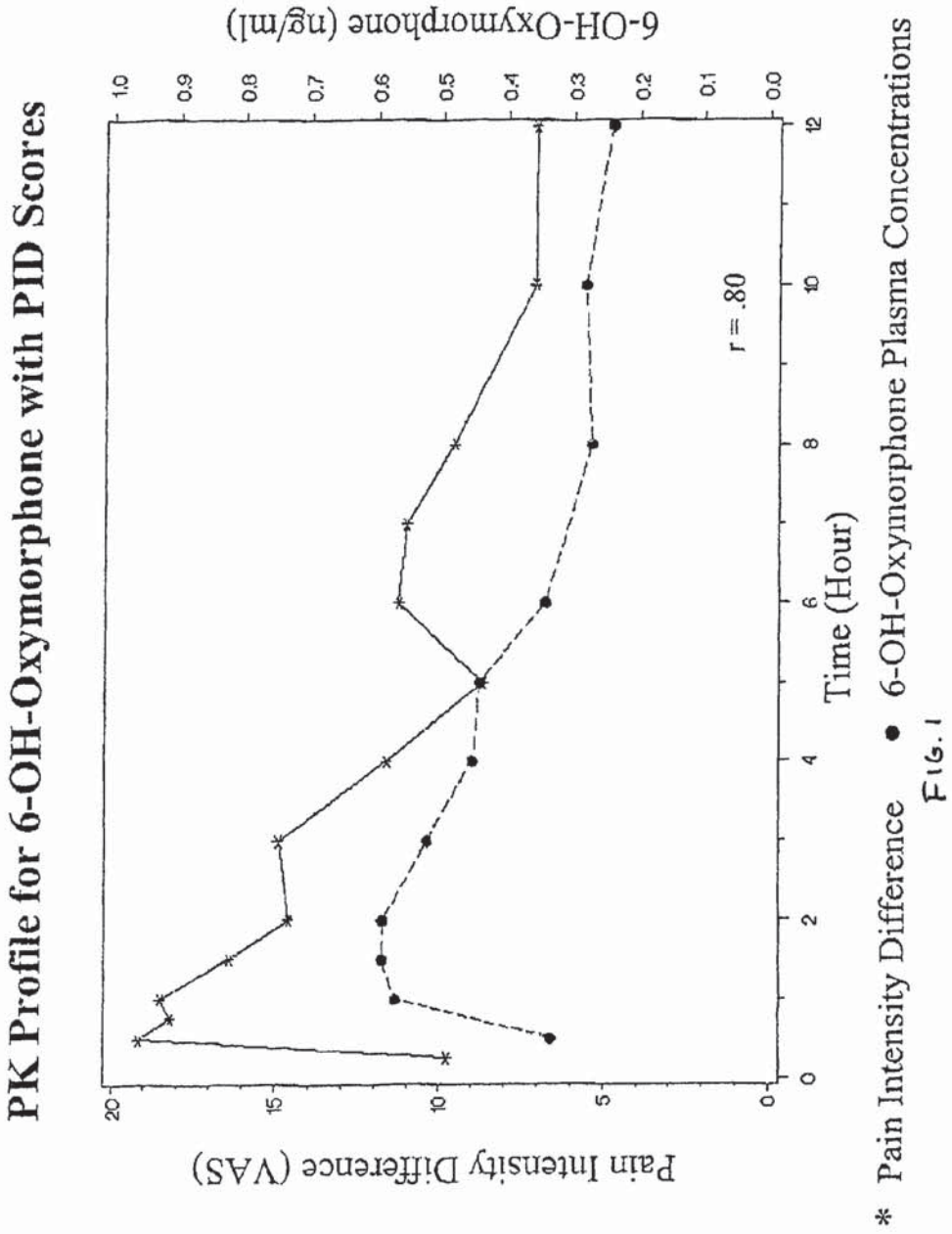
PK Profile for 6-OH-Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
6-OH-Oxymorphone (ng/ml)
Time (Hour)
r = .80
0
5
10
15
20
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
2
4
6
8
10
12
* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

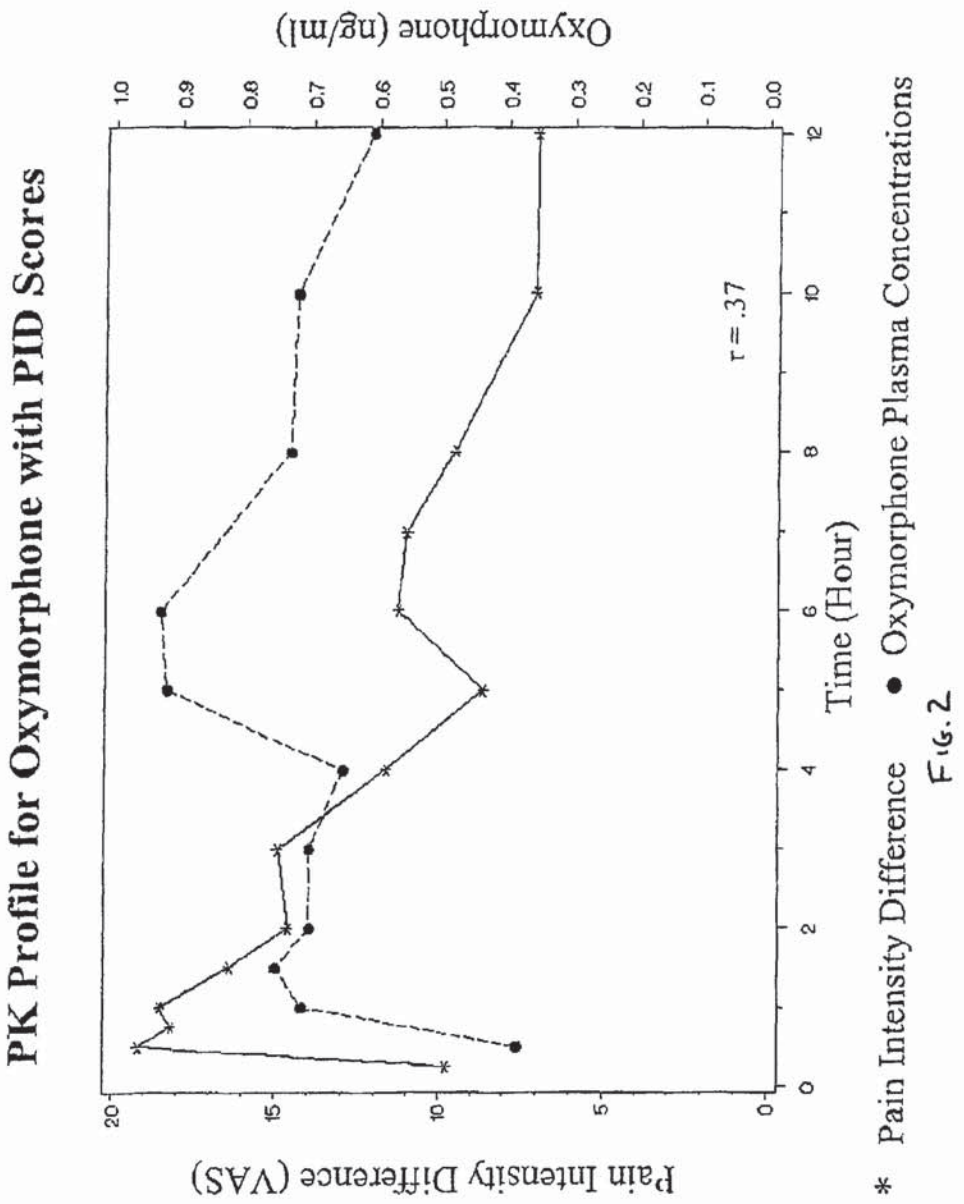
PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference • Oxymorphone Plasma Concentrations

FIG. 2

PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores

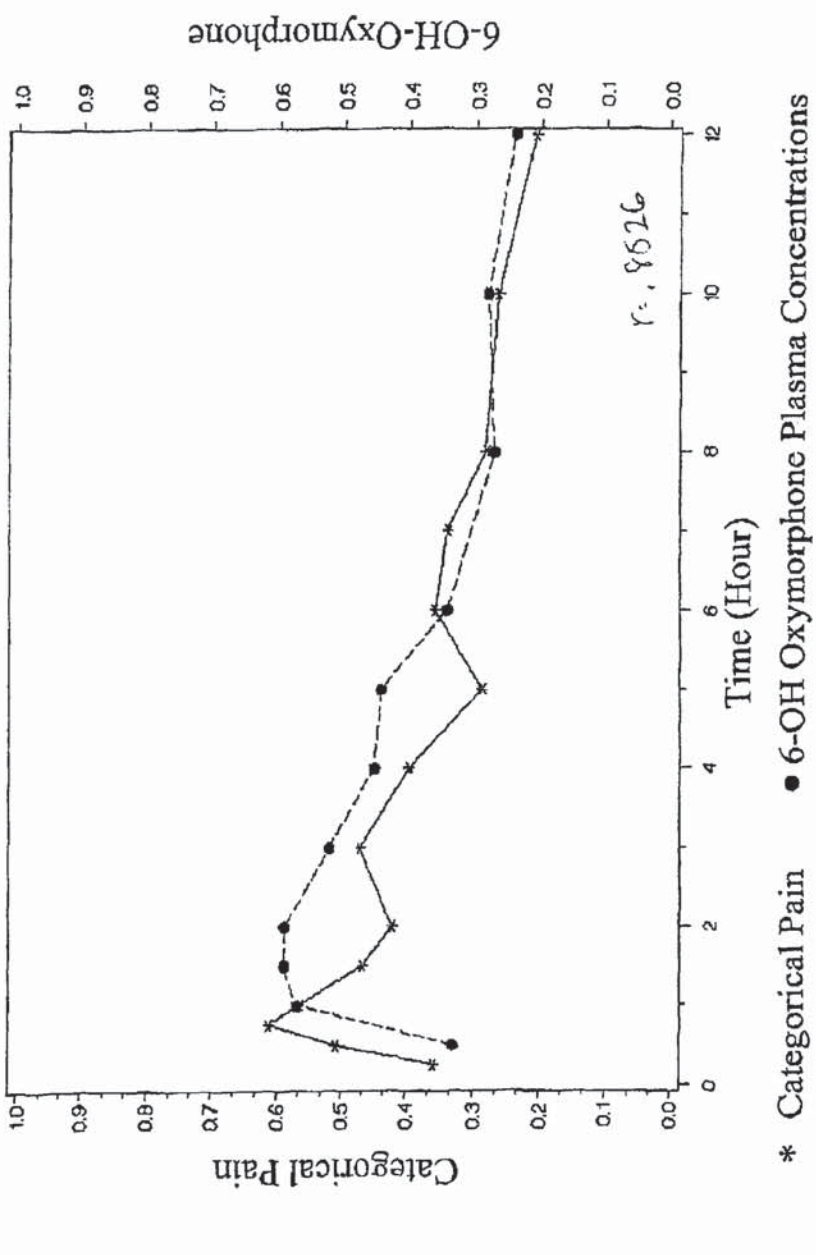

FIG. 3

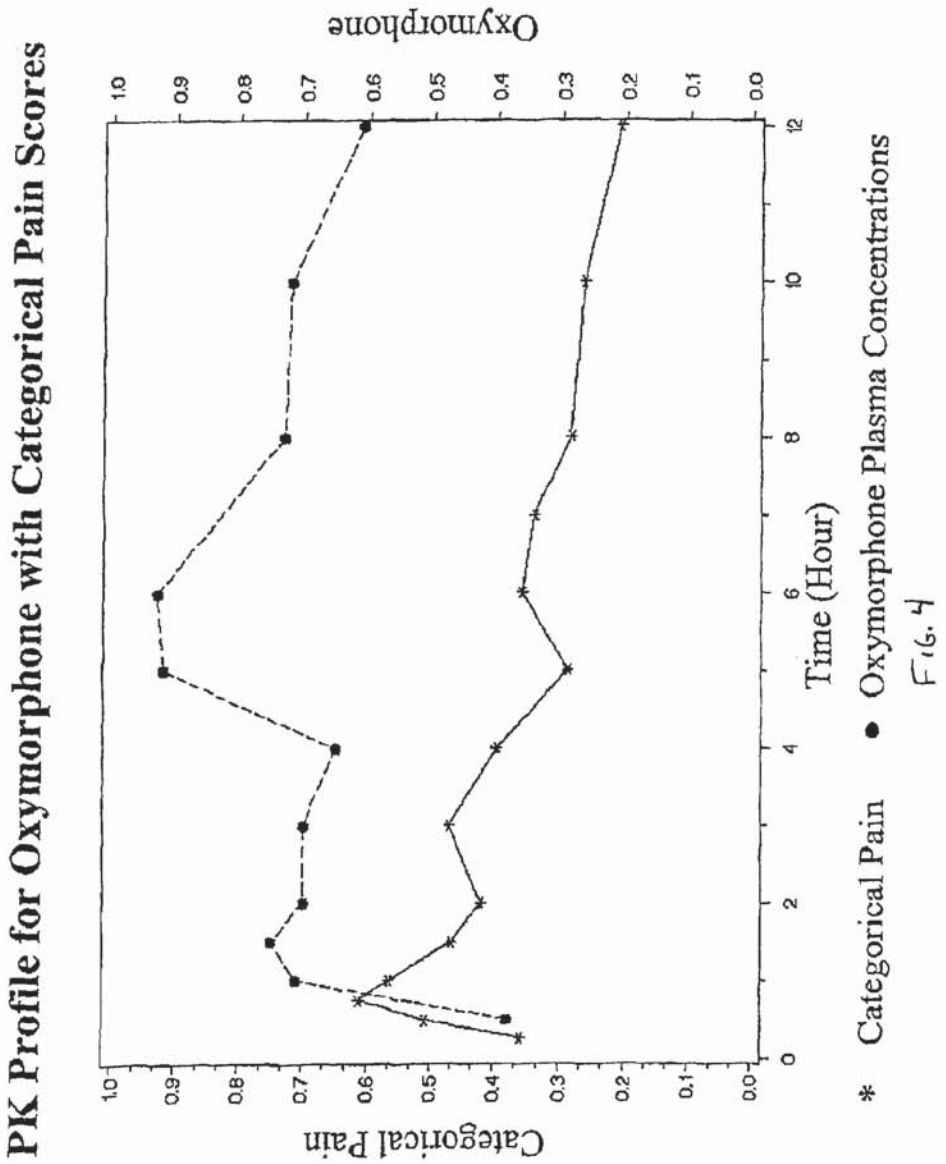
PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
• Oxymorphone Plasma Concentrations

FIG. 4

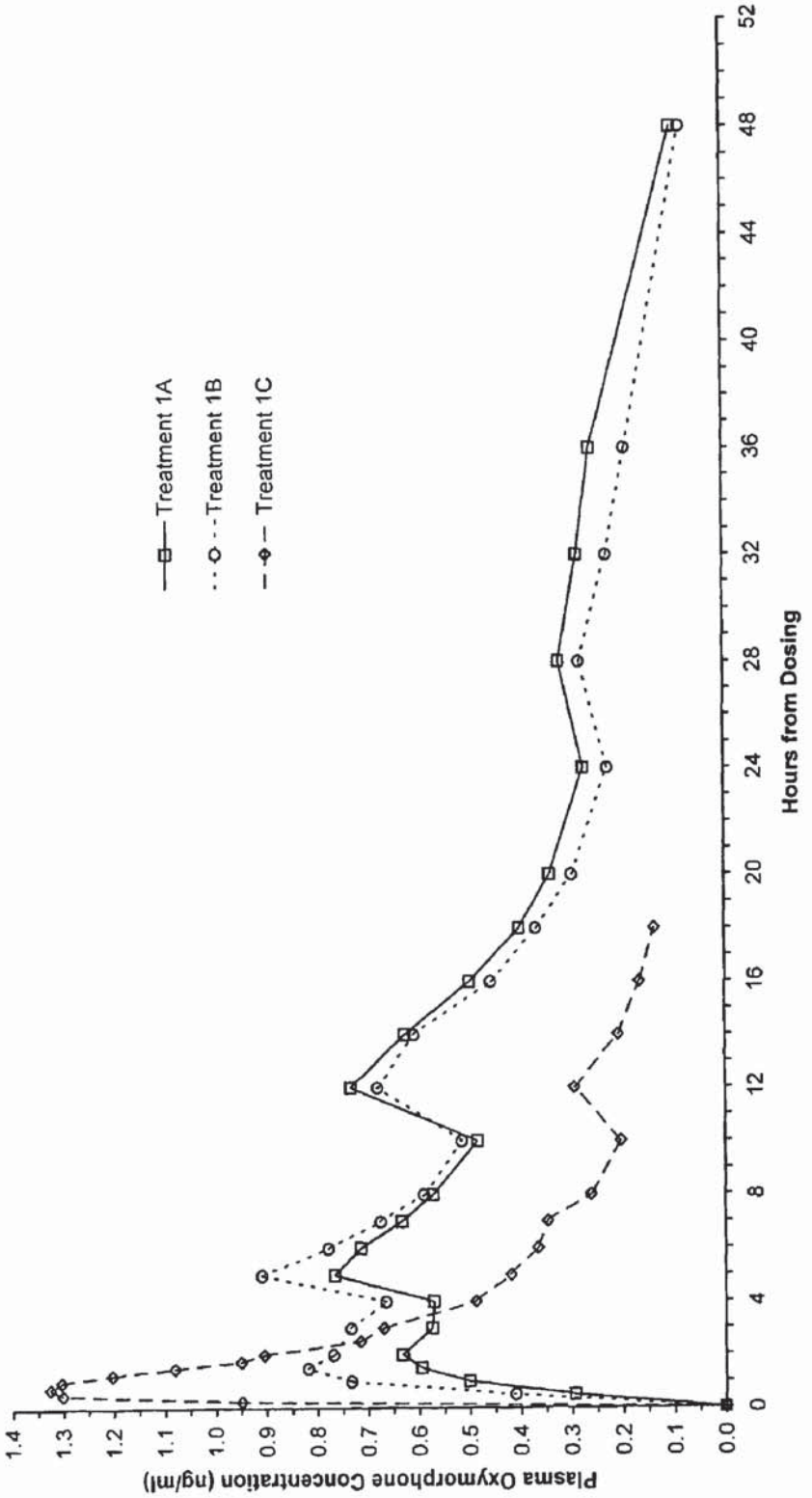
Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

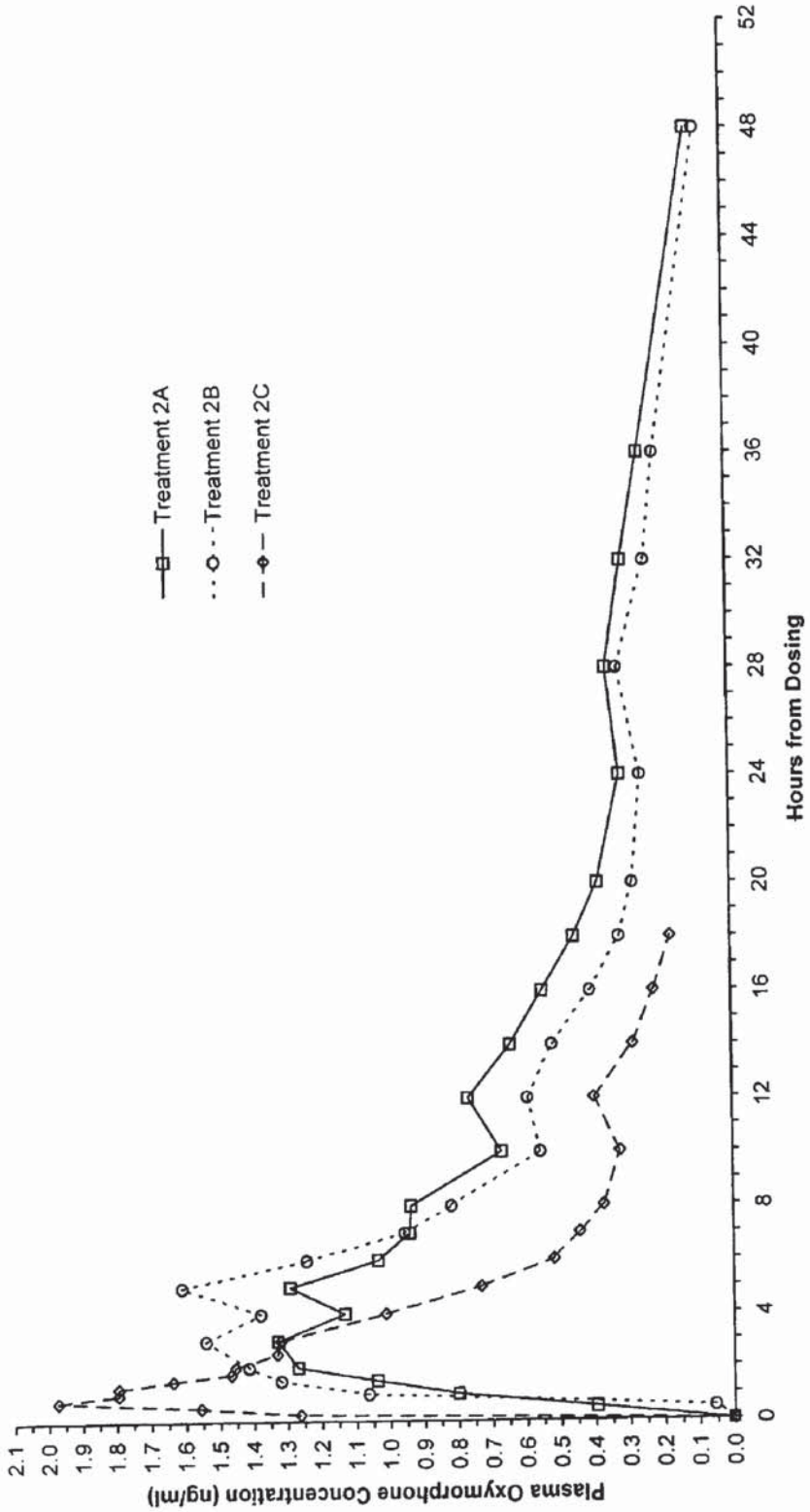
Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6

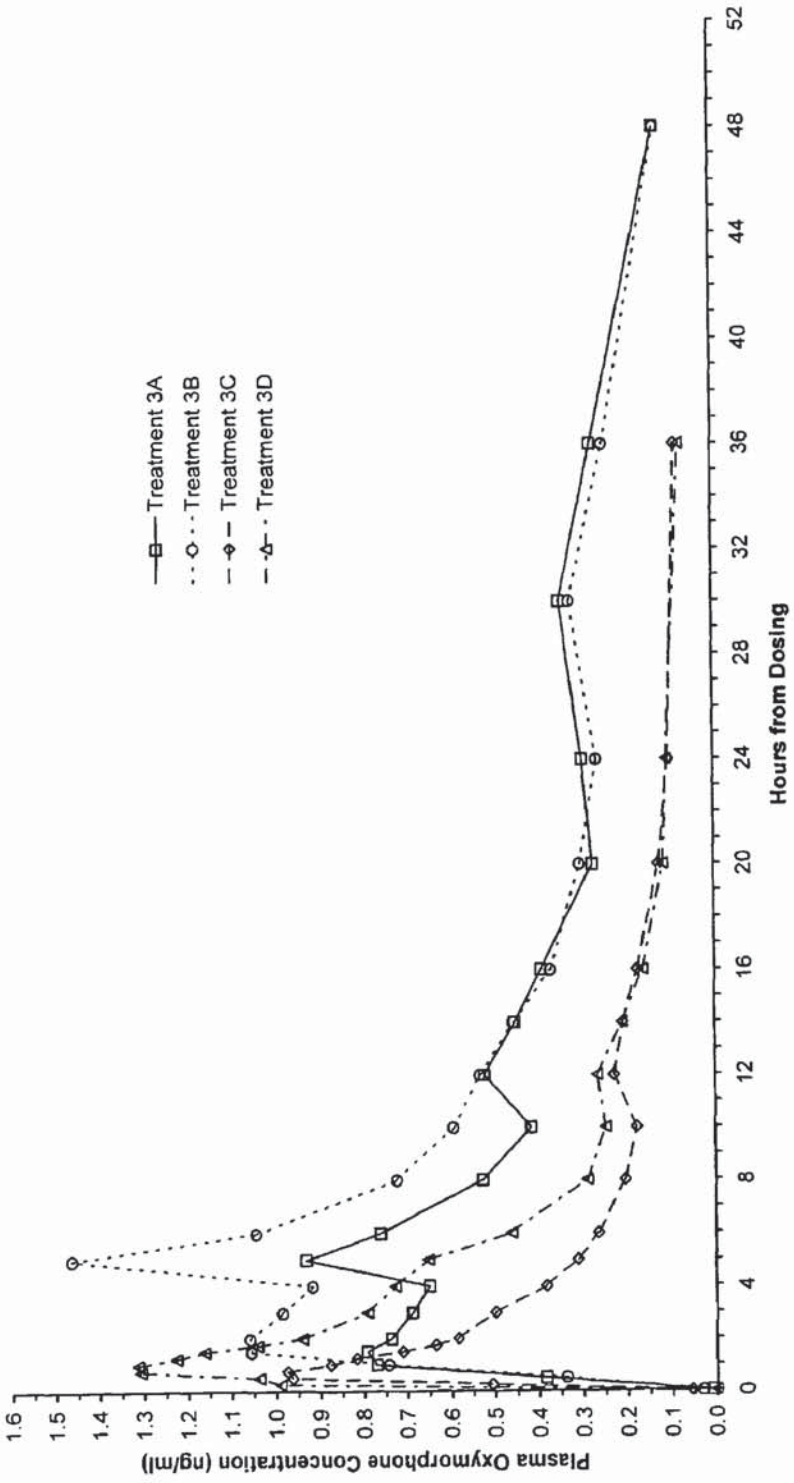
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 7

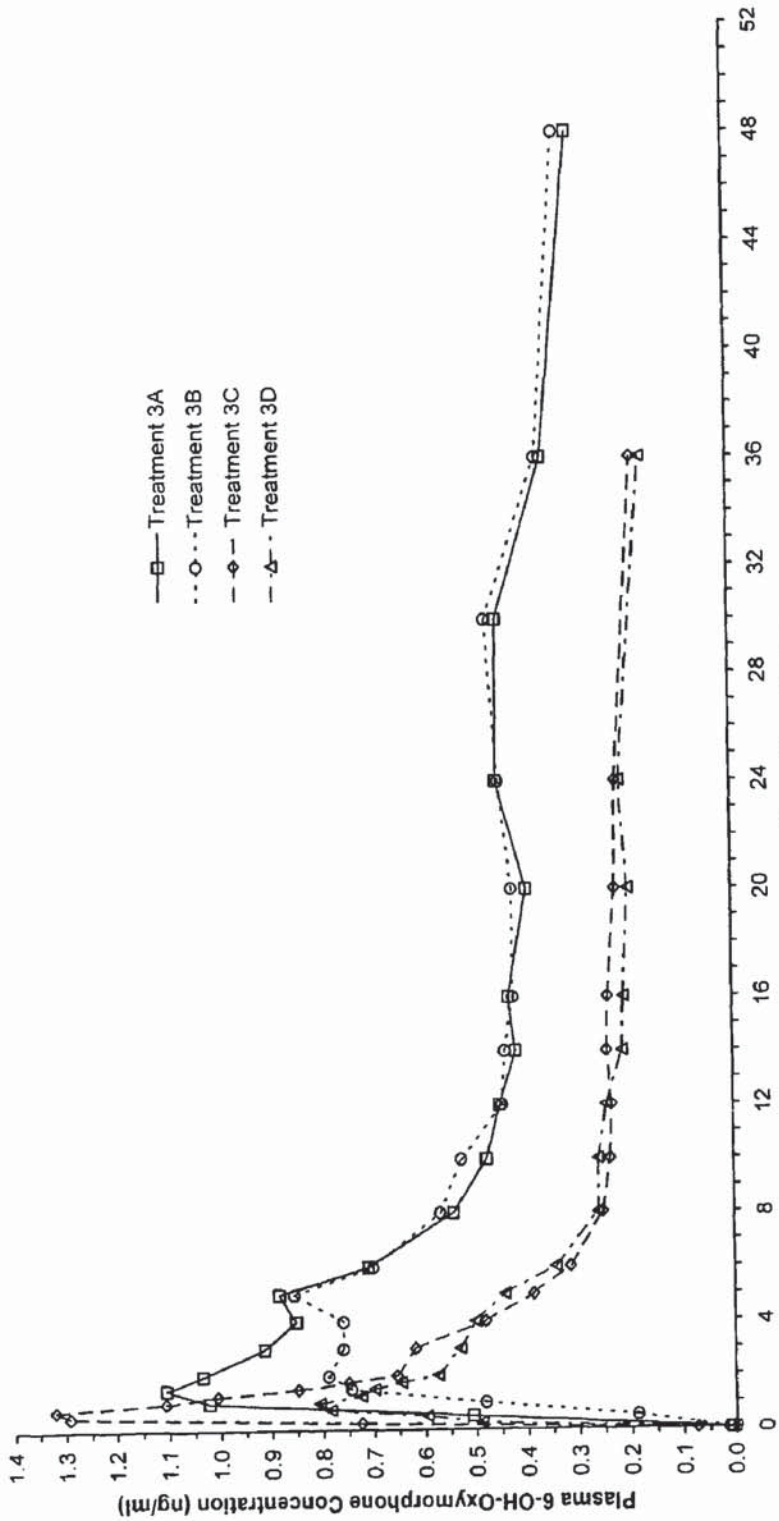
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma 6-OH-Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 8

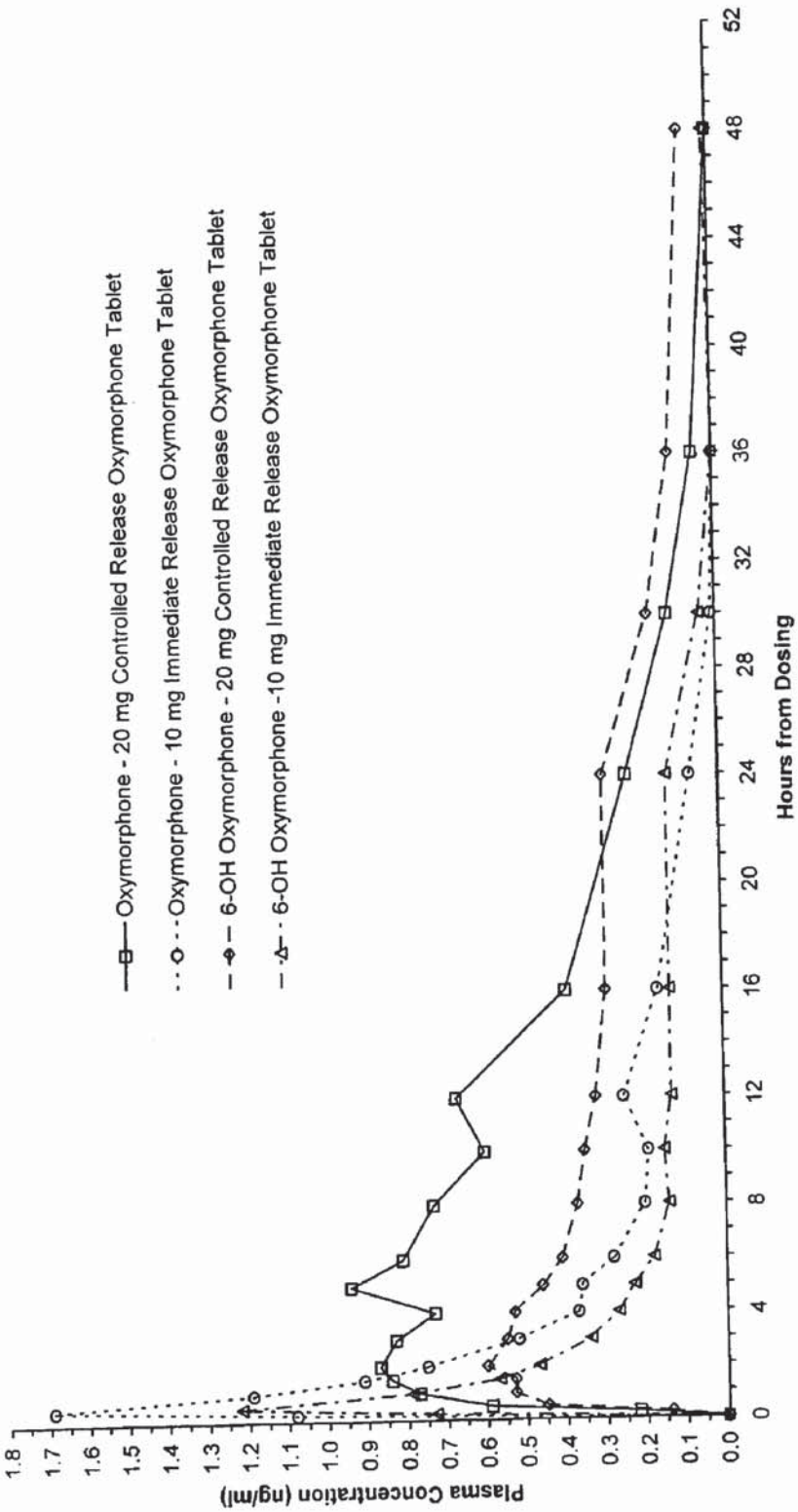
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

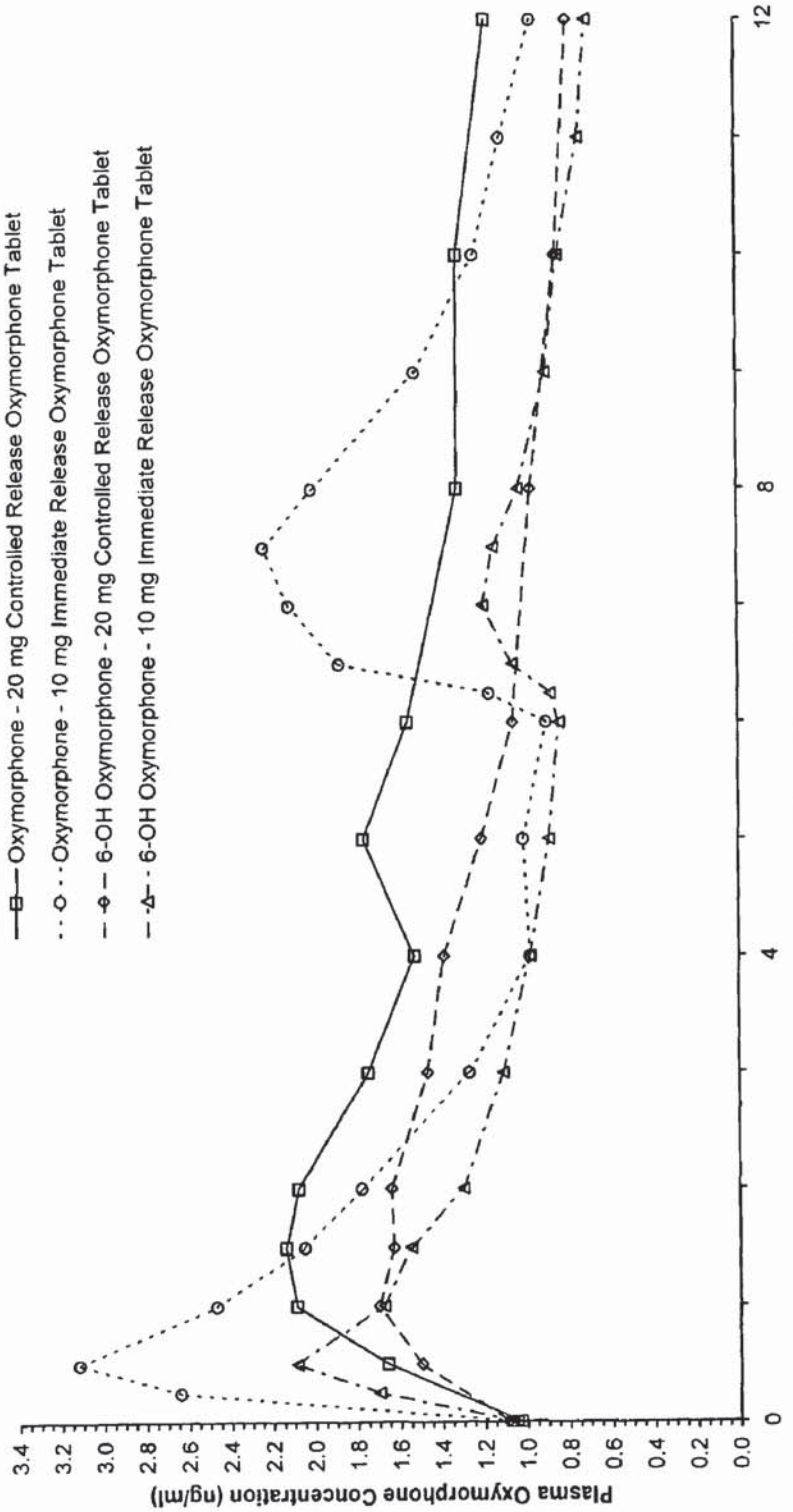
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
4
8
12
Hours from Dosing

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values

reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce nontoxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. **1-2** show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according, to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
$AUC_{(0-inf)}$	Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)} = AUC_{(0-t)} + Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.
$AUC_{(0-24)}$	Partial area under the drug concentration-time curve from time zero to 24 hours.
C_{max}	Maximum observed drug concentration.
T_{max}	Time of the observed maximum drug concentration.
K_{el}	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1—Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. **5**. In both Table 5 and FIG. **5**, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 ± 0.203	1.121 ± 0.211	1.108 ± 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-18)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 ± 0.098	0.783 ± 0.117	0.944 ± 0.110

Study 2—Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. **6**. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 ± 0.187	0.949 ± 0.154	1.148 ± 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}18)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 ± 0.105	0.694 ± 0.124	1.012 ± 0.175

As may be seen from tables 5 and 10 and FIGS. **1** and **2**, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T max much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3—One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. **7**. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.56	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
1.040 ± 0.1874	0.8863 ± 0.2569	1.368 ± 0.4328	1.169 ± 0.2041

TABLE 16

Relative Bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
0.9598 ± 0.2151	0.8344 ± 0.100	1.470 ± 0.3922	1.299 ± 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max}(approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxyoxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under the fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxyoxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ration for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-values duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxyoxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normal-

ized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicted similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment.

Bioavailability of 6-hydroxyoxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max}, was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. **8**. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877

TABLE 17-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma 6-Hydroxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(o-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(o-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4—Controlled Release 20 mg vs. Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. **9** shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed

by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. **9** in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. **10** shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. **10** in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88

TABLE 20-continued

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxy-morphone	6-OH-oxymorphone	oxymor-phone	6-OH-oxymorphone
$AUC_{(o-t)}$	14.74	11.54	7.10	5.66
$AUC_{(o-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½ (hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(o-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(o-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma, concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified, using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5—Controlled Release 40 mg vs. Immediate Release 4.times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times. 10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(o-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(o-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(o-inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(o-24)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(o-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(o-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

2. The pharmaceutical composition of claim **1** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test.

3. The pharmaceutical composition of claim **1** wherein at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

4. The pharmaceutical composition of claim **1** wherein the controlled release delivery system comprises a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid.

5. The pharmaceutical composition of claim **1** wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

6. The pharmaceutical composition of claim **5** wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

7. The pharmaceutical composition of claim **5** wherein the heteropolysaccharide comprises xanthan gum or deacylated xanthan gum.

8. The pharmaceutical composition of claim **5** wherein the agent capable of cross-linking the heteropolysaccharide comprises a homopolysaccharide gum.

9. The pharmaceutical composition of claim **8** wherein the homopolysaccharide gum comprises locust bean gum.

10. The pharmaceutical composition of claim **1** wherein the controlled release delivery system further comprises a hydrophobic polymer.

11. The pharmaceutical composition of claim **10** wherein the hydrophobic polymer comprises an alkylcellulose.

12. The pharmaceutical composition of claim **8** further comprising a cationic cross-linking agent.

13. The pharmaceutical composition of claim **12** wherein the cationic cross-linking agent is selected from calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and combinations thereof.

14. The pharmaceutical composition of claim **13** wherein the cationic cross-linking agent is present in an amount of about 0.5% to about 16%, by weight of the composition.

15. The pharmaceutical composition of claim **5** wherein the weight ratio of heteropolysaccharide to oxymorphone or pharmaceutically acceptable salt thereof is about 10:1 to about 1:10.

16. The pharmaceutical composition of claim **1** wherein oxymorphone or pharmaceutically acceptable salt thereof is present in an amount of about 5 mg to about 80 mg.

17. The pharmaceutical composition of claim **5** wherein the controlled release delivery system comprises about 10% to about 99% of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, about 1% to about 20% of a cationic crosslinking agent, and about 0% to about 89% of other ingredients which qualify as an inert pharmaceutical diluent, by total weight of the controlled release delivery system.

18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **1** comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8

at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

20. The method of claim **18** wherein upon oral administration of the composition the oxymorphone $AUC_{(o\text{-}inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

* * * * *

EXHIBIT C

(12) **United States Patent**
Kao et al.

(10) **Patent No.: US 8,329,216 B2**
(45) **Date of Patent: *Dec. 11, 2012**

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

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(73) Assignee: **Endo Pharmaceuticals Inc.**, Chadds Ford, PA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1192 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/427,438**

(22) Filed: **Jun. 29, 2006**

(65) **Prior Publication Data**

US 2007/0098794 A1 May 3, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on Jul. 3, 2002.

(60) Provisional application No. 60/329,445, filed on Oct. 15, 2001, provisional application No. 60/329,432, filed on Oct. 15, 2001, provisional application No. 60/303,357, filed on Jul. 6, 2001, provisional application No. 60/329,444, filed on Oct. 15, 2001.

(51) **Int. Cl.**

A61K 9/22	(2006.01)
A61K 9/34	(2006.01)
A61K 9/36	(2006.01)

(52) **U.S. Cl.** **424/464**; 424/468; 424/470; 424/479; 424/481; 424/482; 424/486

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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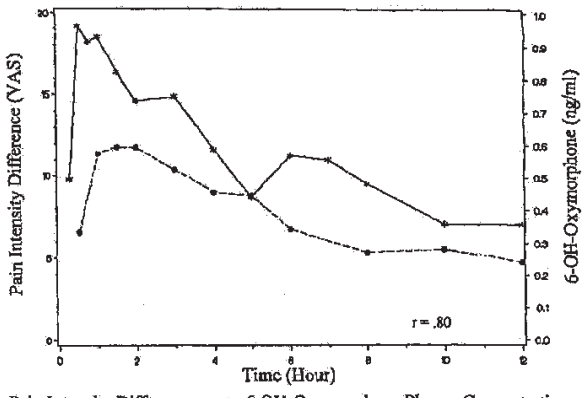
(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

82 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



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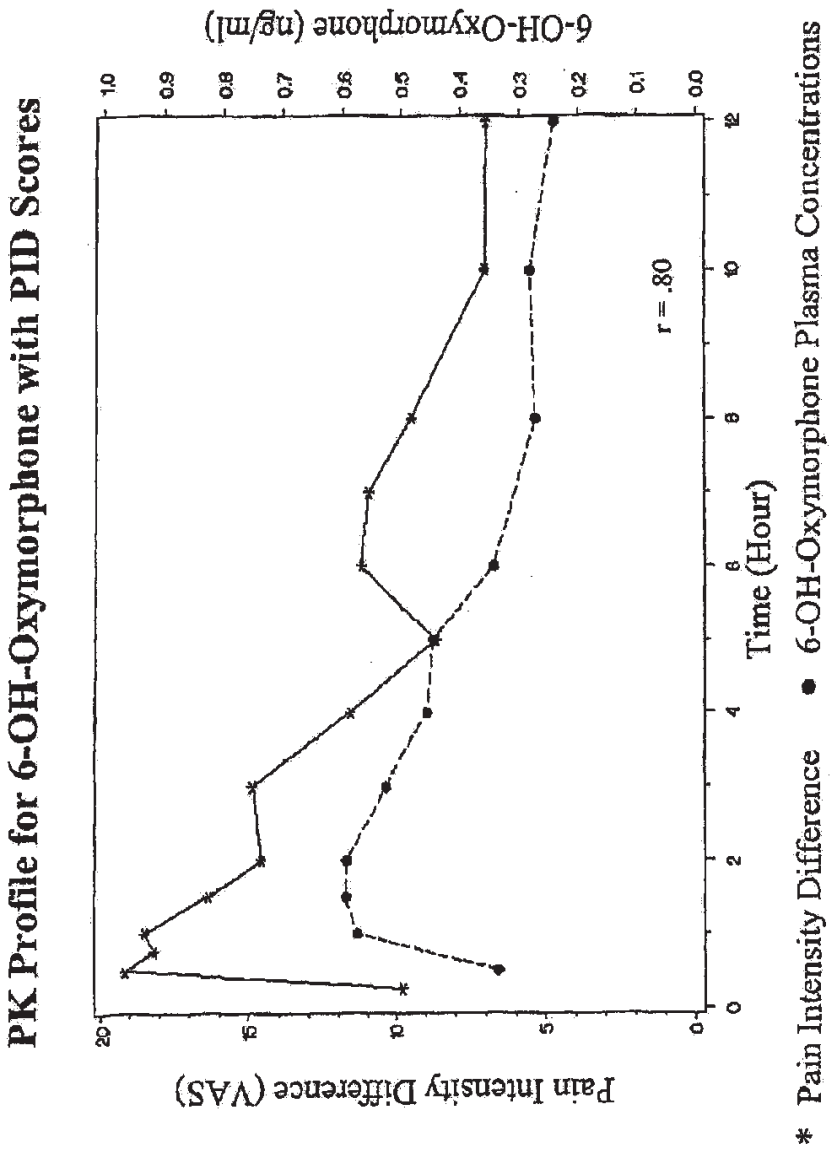
PK Profile for 6-OH-Oxymorphone with PID Scores
6-OH-Oxymorphone (ng/ml)
Pain Intensity Difference (VAS)
Time (Hour)
r = .80
* Pain Intensity Difference
● 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

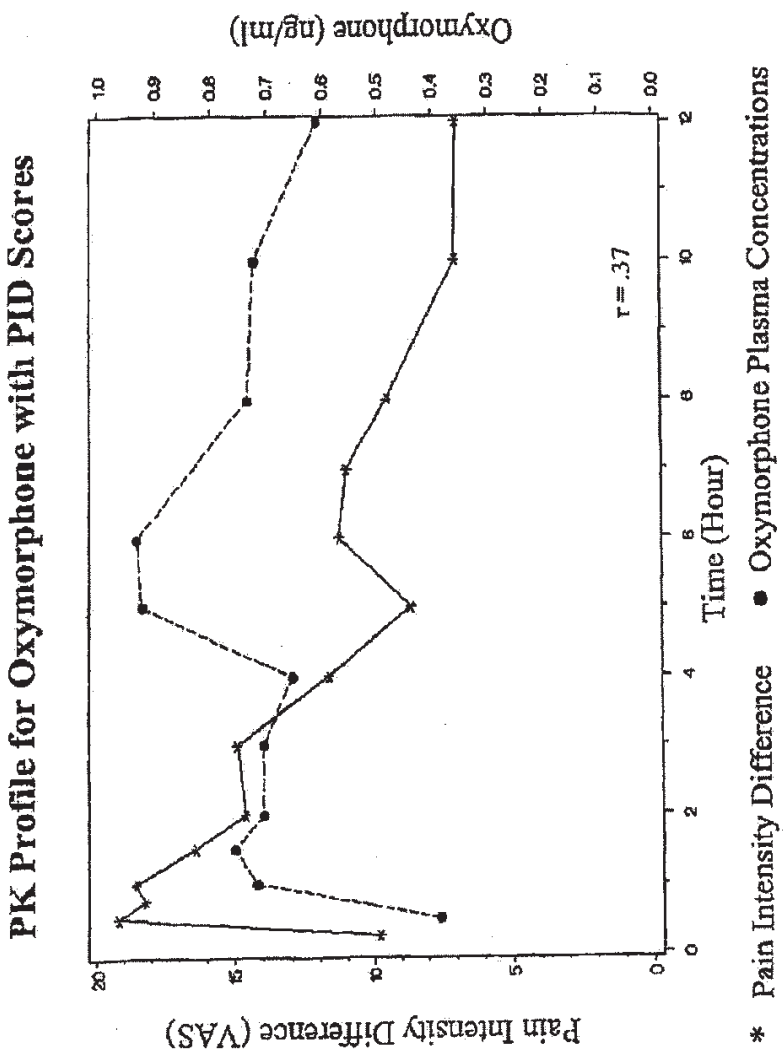
PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference
• Oxymorphone Plasma Concentrations

FIG. 2

PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores

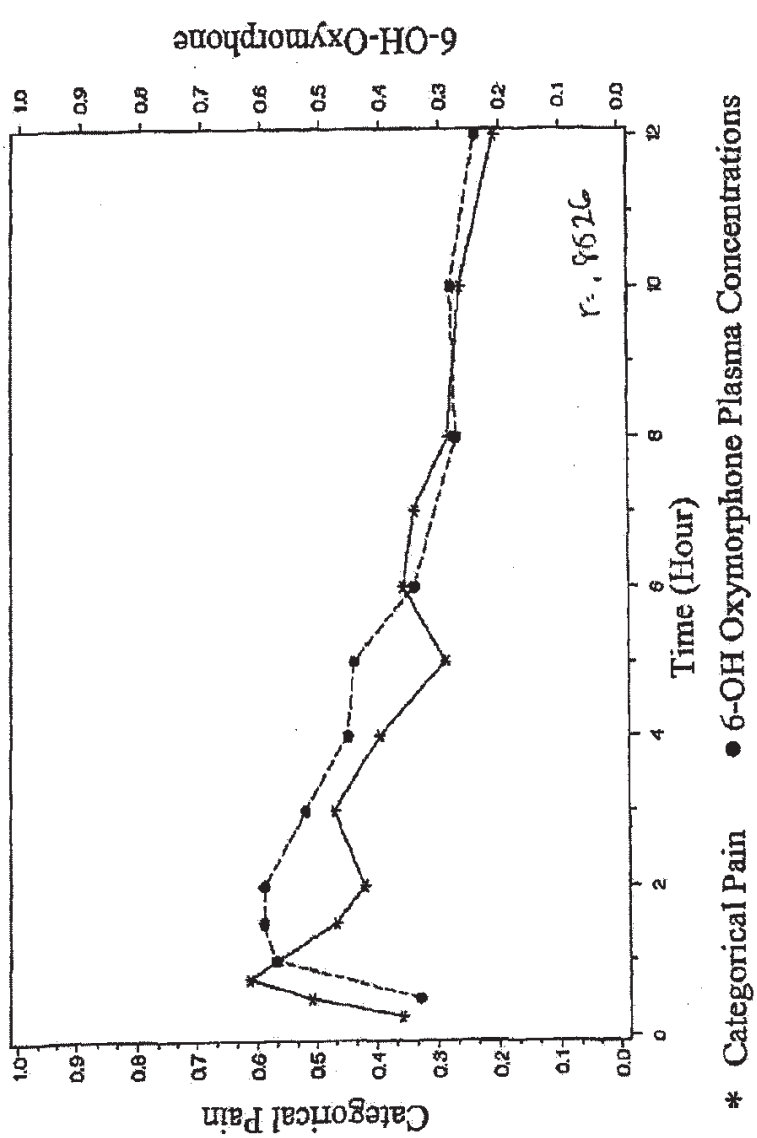

Fig. 3

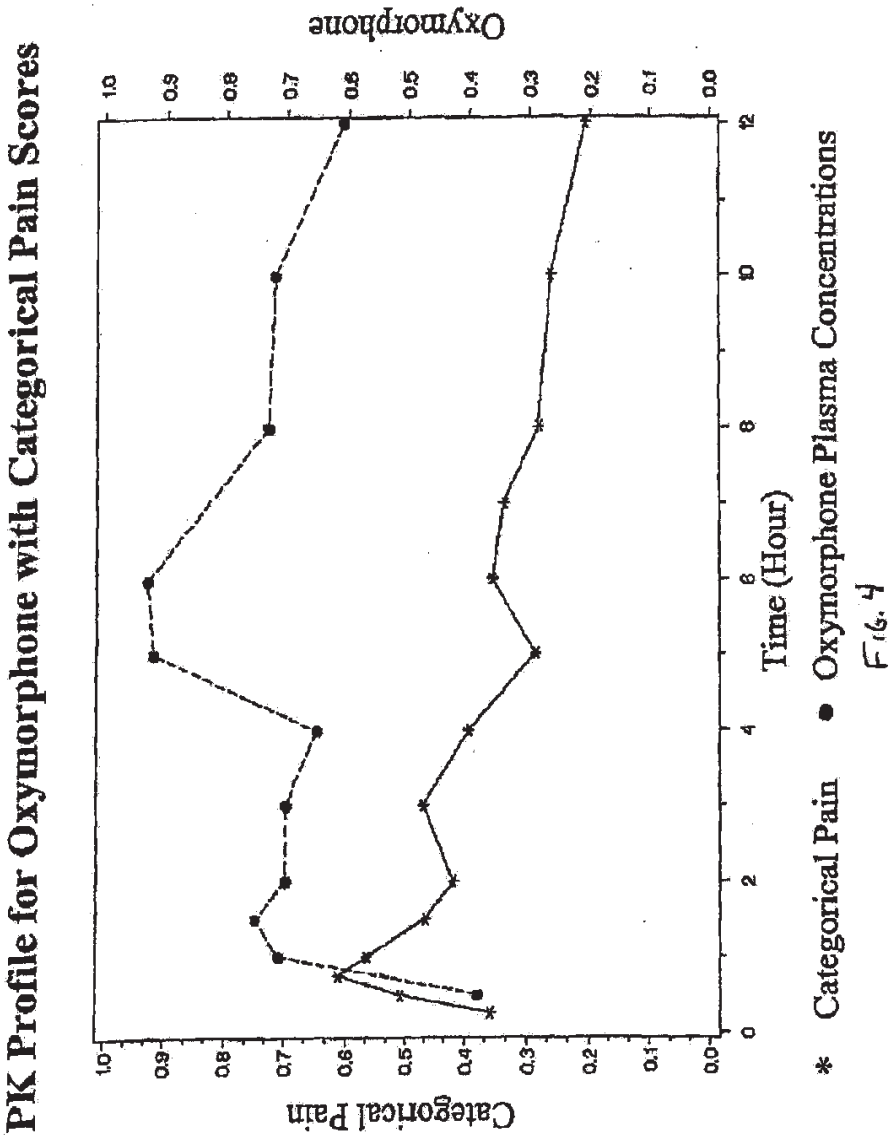
PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
● Oxymorphone Plasma Concentrations

FIG. 4

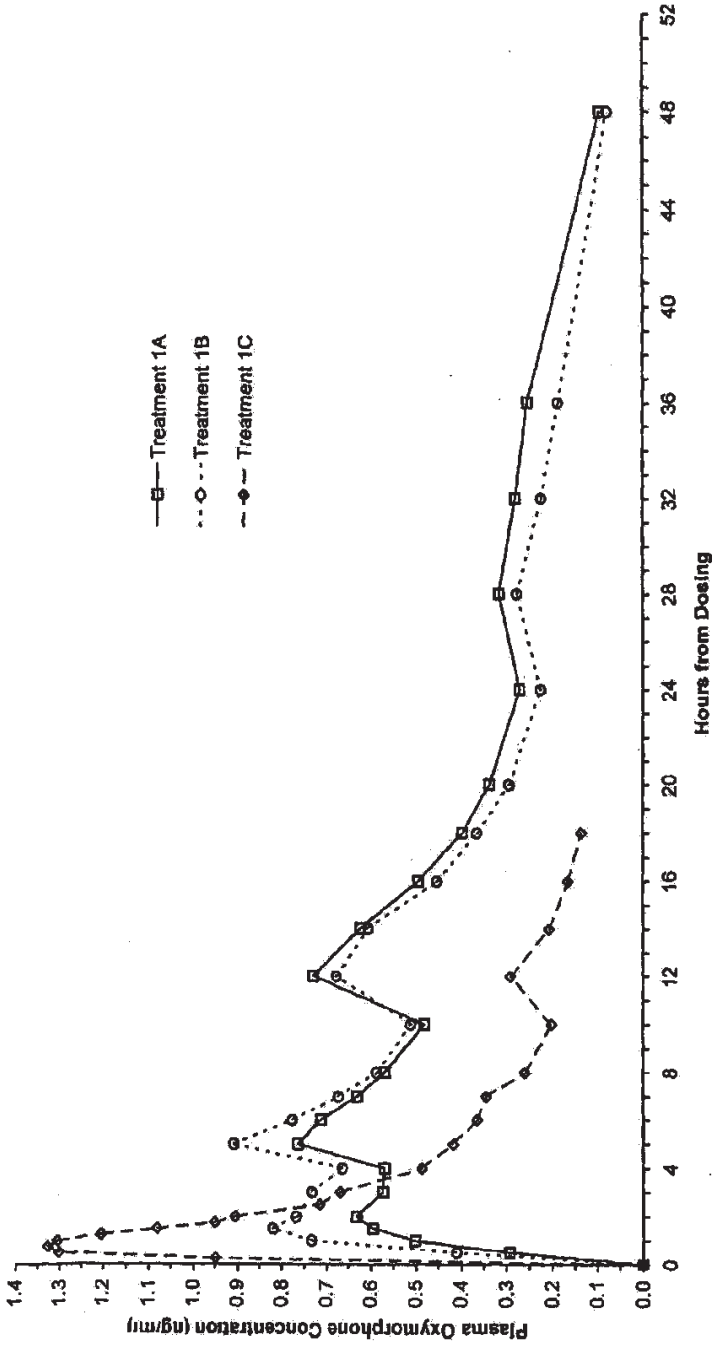
Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

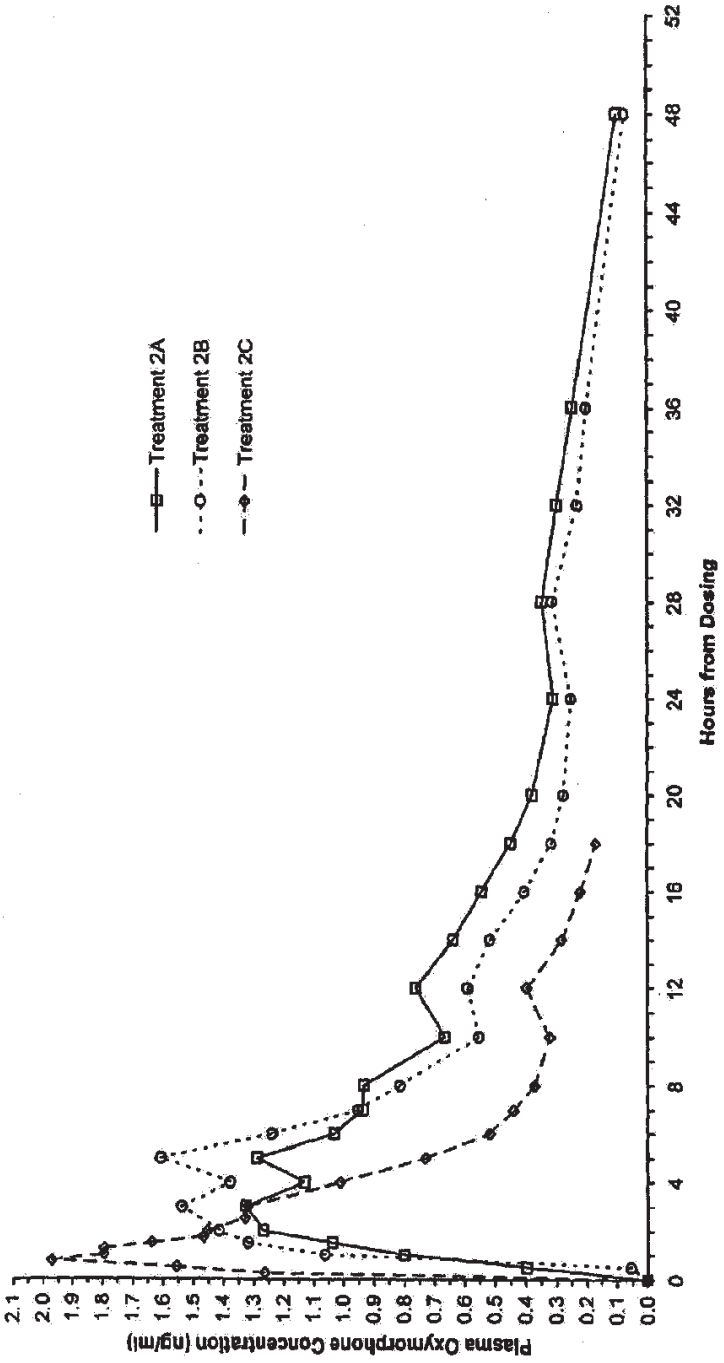
Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6

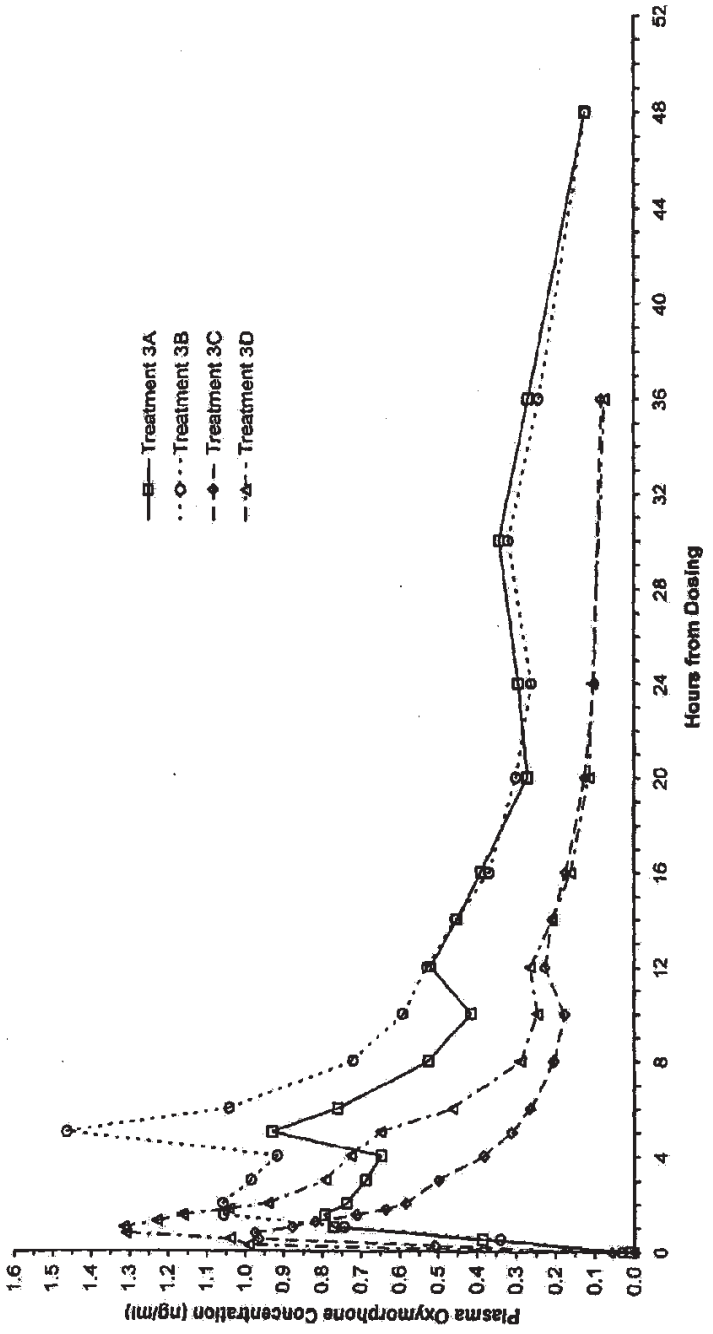
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 7

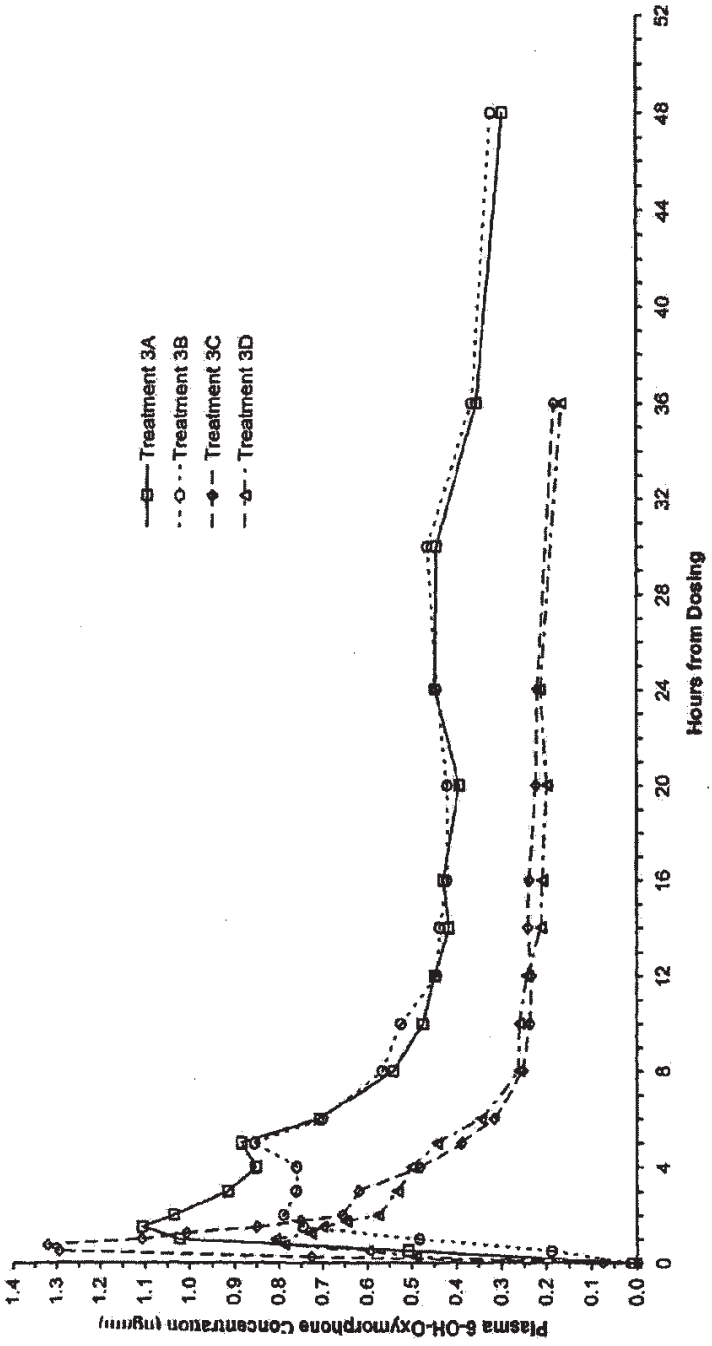
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Hours from Dosing
Plasma 6-OH-Oxymorphone Concentration (ng/mL)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 8

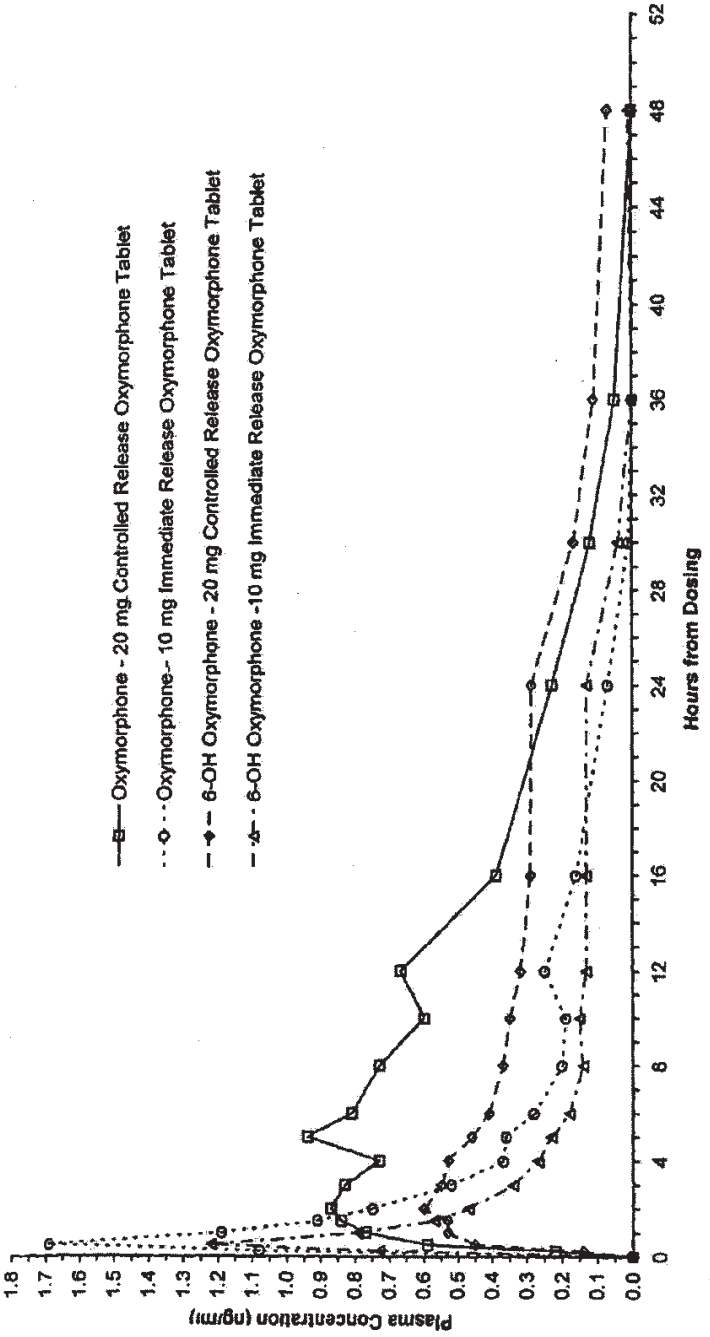
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone- 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

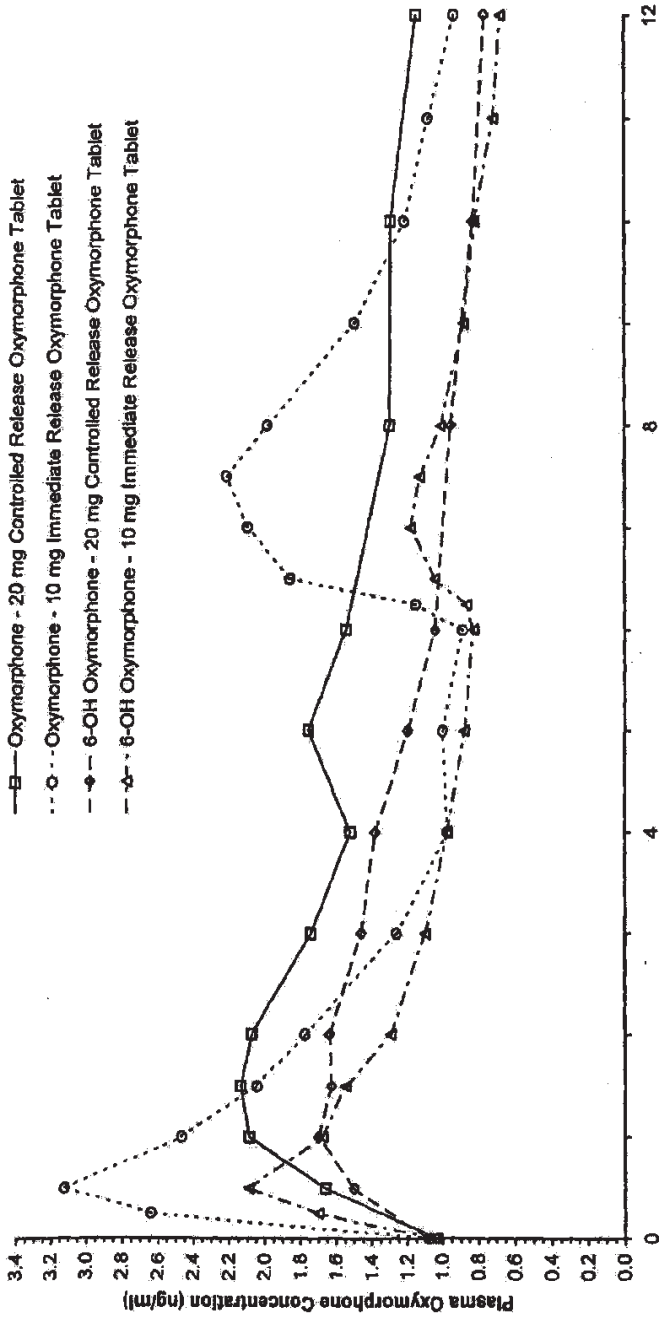
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
0
4
8
12

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. 1-2 show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10^6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$ Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.

$AUC_{(0-inf)}$ Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)}=AUC_{(0-t)}+Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.

$AUC_{(0-24)}$ Partial area under the drug concentration-time curve from time zero to 24 hours.

C_{max} Maximum observed drug concentration.

T_{max} Time of the observed maximum drug concentration.

K_{el} Elimination rate constant based on the linear regression of the terminal linear portion of the LN (concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1-Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 ± 0.203	1.121 ± 0.211	1.108 ± 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-tlast)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 ± 0.098	0.783 ± 0.117	0.944 ± 0.110

Study 2-Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 .±. 0.187	0.949 .±. 0.154	1.148 .±. 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}tf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 .±. 0.105	0.694 .±. 0.124	1.012 .±. 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T_{max} much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3-One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.65	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
1.040 .±. 0.1874	0.8863 .±. 0.2569	1.368 .±. 0.4328	1.169 .±. 0.2041

TABLE 16

Relative bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 2C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
0.9598 .±. 0.2151	0.8344 .±. 0.100	1.470 .±. 0.3922	1.299 .±. 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max} (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was

later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicated similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability of 6-hydroxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(0-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(0-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4-Controlled Release 20 mg vs Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg

controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. 9 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
$AUC_{(o-t)}$	14.74	11.54	7.10	5.66
$AUC_{(o-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½(hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(0-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(0-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5-Controlled Release 40 mg vs Immediate Release 4.Times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times.10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24

TABLE 22-continued

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0\text{-}t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0\text{-}inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(0\text{-}24)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27

TABLE 26-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma
6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(0\text{-}t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(0\text{-}inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An oral controlled release oxymorphone formulation, comprising:
   a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and
   b. a hydrophilic material,

wherein upon oral administration of the formulation to a subject in need of an analgesic effect:
   (i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;
   (ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;
   (iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;
   (iv) the duration of the analgesic effect is through at least about 12 hours after administration; and
   (v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

2. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

3. The formulation of claim 1 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

4. The formulation of claim 3 wherein the gum is selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

5. The formulation of claim 1 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

6. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

7. The formulation of claim 1 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

8. The formulation of claim 7 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

9. The formulation of claim 7 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

10. The formulation of claim 7 wherein the cross-linking agent is a homopolysaccharide gum.

11. The formulation of claim 1 further comprising a hydrophobic polymer.

12. A method of treating pain in a subject in need thereof, the method comprising the step of administering to the subject the formulation of claim 1.

13. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and controlled release granules comprising a hydrophilic material and one or more optional excipients; and

b. directly compressing the mixture of (a) to form the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

14. The tablet preparation of claim 13 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

15. The tablet preparation of claim 13 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

16. The tablet preparation of claim 13 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

17. The tablet preparation of claim 13 wherein the hydrophilic material is hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

18. The tablet preparation of claim 13 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

19. The tablet preparation of claim 18 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

20. The tablet preparation of claim 19 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

21. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and

b. forming the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

22. The tablet of claim 21 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

23. The tablet of claim 21 wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

24. The tablet of claim 21, wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

25. The tablet of claim 21, wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

26. The tablet of claim 21, wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

27. The tablet of claim 21, wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

28. The tablet of claim 21, wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

29. The tablet of claim 21, wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

30. The tablet of claim 21, wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

31. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

32. The method of claim **31** wherein the dosage form comprises about 40 mg oxymorphone or a pharmaceutically acceptable salt thereof, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

33. The method of claim **31** wherein the dosage form comprises about 20 mg oxymorphone or a pharmaceutically acceptable salt thereof.

34. The method of claim **31** wherein the dosage form comprises about 20 mg to about 40 mg oxymorphone hydrochloride.

35. The method of claim **31** wherein the difference in the oxymorphone area under the curve ($AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

36. The method of claim **35** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

37. The method of claim **31** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

39. The method of claim **38** wherein the oxymorphone C_{max} is at least about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

40. The method of claim **38** wherein the difference in the oxymorphone area under the curve $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

41. The method of claim **40** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

42. The method of claim **38** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

43. The method of claim **38** wherein the system further comprises a hydrophilic material.

44. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

45. The method of claim **44** wherein the hydrophilic material is a gum selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

46. The method of claim **43** wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

47. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

48. The method of claim **43** wherein the hydrophilic material comprises at least one of:

a. a heteropolysaccharide; or

b. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

c. a mixture of (a), (b) and a polysaccharide gum.

49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°

C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

50. The composition of claim **49** wherein upon oral administration thereof the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

51. The composition of claim **49** wherein the dosage form comprises about 40 mg oxymorphone, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

52. The composition of claim **49** wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

53. The composition of claim **52** wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

54. The composition of claim **49** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

56. The composition of claim **55**, wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions.

57. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

58. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

59. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

60. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

61. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

62. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

63. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

64. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

65. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

67. The composition of claim **66** wherein the blood plasma levels comprise two peaks.

68. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect:

(i) the composition provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

69. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an anal-

gesic effect the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

70. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect the blood plasma levels of oxymorphone comprise a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration.

71. The composition of claim **66** wherein the composition is in the form of a tablet and about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

73. The pharmaceutical composition of claim **72** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

74. The pharmaceutical composition of claim **72** wherein at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

75. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises one or peaks.

76. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration; and wherein

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test,

wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0\text{-}inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

78. The pharmaceutical composition of claim **77** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect the blood plasma level of oxymorphone displays two or three peaks over about the first 12 hours after administration; and

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

79. The pharmaceutical composition of claim **77** wherein about 58% to about 66%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

80. The pharmaceutical composition of claim **77** wherein about 85% to about 96%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

81. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **72** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof, wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0\text{-}inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **77** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

* * * * *

EXHIBIT M

UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of	)	
Impax Laboratories, Inc., a corporation,	)	DOCKET NO. 9373
Respondent.	)	

Complaint Counsel's Responses to Respondent Impax Laboratories, Inc.'s First Set of Requests for Admission

Pursuant to Rule 3.32 of the Federal Trade Commission's Rules of Practice, Complaint Counsel hereby responds to Respondent Impax Laboratories, Inc.'s Requests for Admission, dated July 24, 2017. Complaint Counsel reserves the right to supplement and amend its objections and responses as necessary.

General Objections Applicable to All Topics

1. Complaint Counsel objects to each request and to the Definitions and Instructions to the extent that they purport to impose upon Complaint Counsel any obligation beyond those imposed by the FTC Rules of Practice.

2. Complaint Counsel objects to each request to the extent that it is vague, ambiguous, or imprecise as to the information sought. Where vague, ambiguous, or imprecise terms are used, Complaint Counsel will only provide information that is reasonably responsive to the request.

3. Complaint Counsel objects to each request to the extent it calls for a legal interpretation or legal conclusion.

4. Complaint Counsel objects to each request to the extent that it presents a hypothetical and asks for an admission about events that may not occur.

5. Complaint Counsel objects to each request to the extent that it seeks information outside the scope of Complaint Counsel's knowledge, custody, or control.

6. None of the specific objections and responses are an admission of the relevance or admissibility of the information requested.

Specific Objections and Responses to Individual Requests for Admission

Request No. 1: Admit that in *In the Matter of King Pharmaceuticals, Inc. and Alpharma, Inc.*, Dkt. No. C-4246, the Federal Trade Commission alleged a relevant market consisting of "the manufacture and sale of oral [long-acting opioids]," which the Federal Trade Commission defined to include oxycodone, morphine sulfate, and oxymorphone.

Response and Specific Objections to Request No. 1:

Complaint Counsel denies Request No. 1. The complaint in *In the Matter of King Pharmaceuticals, Inc. and Alpharma, Inc.* alleged that "the relevant line of commerce in which to analyze the effects of the Acquisition is no broader than the manufacture and sale of LAOs, and includes the narrower market for oral long-acting morphine sulfate . . . ." (Dkt. No. C-4246).

Request No. 2: Admit that the January 1, 2013 license entry date contained in the Settlement & License Agreement is 16 years before the expiration of all patents covered by the license and /or the covenant not to sue in that agreement.

Response and Specific Objections to Request No. 2:

Complaint Counsel objects to Request No. 2 on the ground that it imprecisely specifies the information sought and is compound.

Complaint Counsel denies Request No. 2. It is not clear on the face of the Settlement & License which patents are covered by the license and/or covenant not to sue, and that issue is currently the subject of litigation between Endo and Impax.

Request No. 3: Admit that Impax is the only company that is currently selling a generic version of Opana ER in the United States.

Response and Specific Objections to Request No. 3:

Complaint Counsel admits Request No. 3.

Request No. 4: Admit that on June 8, 2017, the United States Food and Drug Administration publicly requested that Endo withdraw its Reformulated Opana ER product from the market.

Response and Specific Objections to Request No. 4:

Complaint Counsel admits Request No. 4.

Request No. 5: Admit that the United States Food and Drug Administration concluded, in response to a Citizen Petition from Endo, that Endo did not withdraw its Original Opana ER product for safety or efficacy reasons.

Response and Specific Objections to Request No. 5:

Complaint Counsel admits Request No. 5.

Request No. 6: Admit that Endo has publicly announced its intent to stop selling Reformulated Opana ER beginning September 1, 2017.

Response and Specific Objections to Request No. 6:

Complaint Counsel admits Request No. 6.

Request No. 7: Admit that, as of September 1, 2017, Impax's generic oxymorphone ER will be the only FDA-approved form of oxymorphone ER available to consumers in branded or generic form.

Response and Specific Objections to Request No. 7:

Complaint Counsel objects to Request No. 7 on the ground that it is a hypothetical and seeks an admission about future events that may not occur.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny. Complaint Counsel does not know and cannot readily ascertain whether, by September 1, 2017: (1) Endo will stop selling all versions of oxymorphone ER; (2) Endo oxymorphone ER product will still be available for sale by wholesalers or retail pharmacies; (3) Endo will re-introduce its original formulation of oxymorphone ER; or (4) another company will begin selling a version of oxymorphone ER.

Request No. 8: Admit that in *Endo Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC*, 2016 WL 4869946 (D. Del. Oct. 7, 2016), the District Court ruled that Endo's U.S. Patent No. 8,871,779 was valid.

Response and Specific Objections to Request No. 8:

Complaint Counsel objects to this Request on the ground that it fails to correctly identify the case citation for *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*. Complaint Counsel's response assumes that Impax meant to seek an admission related to *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*, 224 F. Supp. 3d 368 (D. Del. Oct. 7, 2016). Complaint Counsel further objects to Request No. 8 on the ground that it is not reasonably expected to yield information relevant to the allegations of the complaint, to the proposed relief, or the defenses of Respondent because it relates to a patent that had not been issued at the time of the Settlement & License Agreement and to a judicial decision that came more than six years after the execution of the Settlement & License Agreement that currently on appeal to the Court of Appeals for the Federal Circuit.

Complaint Counsel admits that the District of Delaware found that defendants had failed to prove that the asserted claims of Endo's U.S. Patent No. 8,871,779 invalid, but that decision does not preclude future parties from challenging the validity of the 8,871,779 patent, nor does it preclude other courts from finding that patent invalid.

Request No. 9: Admit that in *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*, 2015 WL 9459823 (S.D.N.Y. Aug. 18, 2015), the District Court ruled that Endo's U.S. Patent Nos. 8,309,122 and 8,329,216 were valid and infringed.

Response and Specific Objections to Request No. 9:

Complaint Counsel objects to this Request on the ground that it is not reasonably expected to yield information relevant to the allegations of the complaint, to the proposed relief, or the defenses of Respondent because it relates to patents that had not been issued

at the time of the Settlement & License Agreement and to a judicial decision that came over five years after the execution of the Settlement & License Agreement is currently on appeal to the Court of Appeals for the Federal Circuit.

Complaint Counsel admits that the Southern District of New York found that certain asserted claims of Endo's U.S. Patent Nos. 8,309,122 and 8,329,216 were not proved invalid and were infringed by the specific oxymorphone products developed by the defendants in that litigation, but that decision does not preclude future parties from challenging the validity of those patents, introducing a product that does not infringe those patents, or preclude other courts from finding those patents invalid.

Request No. 10: Admit that in *Endo Pharmaceuticals Inc. v. Amneal Pharmaceuticals, LLC*, 2016 WL 1732751 (S.D.N.Y. Apr. 29, 2016), the District Court enjoined Actavis, Inc., Actavis South Atlantic LLC, and Roxane Laboratories, Inc., from making or selling their generic versions of Opana ER prior to the expiration of Endo's U.S. Patent Nos. 8,309,122 and 8,329,216.

Response and Specific Objections to Request No. 10:

Complaint Counsel objects to this Request on the ground that it is not reasonably expected to yield information relevant to the allegations of the complaint, to the proposed relief, or the defenses of Respondent because it relates to patents that had not been issued at the time of the Settlement & License Agreement and to a judicial decision that came over five years after the execution of the Settlement & License Agreement that is currently on appeal to the Court of Appeals for the Federal Circuit.

Complaint Counsel admits that the Southern District of New York enjoined Actavis, Inc., Actavis South Atlantic LLC, and Roxane Laboratories, Inc. from making or selling their generic versions of Opana ER prior to the expiration of Patents Nos. 8,309,122 and 8,239,216, but that decision does not preclude future parties from

challenging the validity of those patents or introducing a product that does not infringe those patents, nor does it preclude other courts from finding those patents invalid.

Request No. 11: Admit that in *Endo Pharmaceuticals Inc. v. Actavis, Inc.*, 743 F.3d 1371 (Fed. Cir. 2014), the Federal Circuit held that Actavis, Inc., Actavis South Atlantic, LLC, and Roxane Laboratories, Inc., did not have express or implied licenses to U.S. Patent Nos. 8,309,122 or 8,329,216, under the terms of their respective settlement agreements with Endo.

Response and Specific Objections to Request No. 11:

Complaint Counsel objects to this Request on the ground that it fails to correctly identify the case citation for *Endo Pharmaceuticals Inc. v. Actavis, Inc.* Complaint Counsel's response assumes that Impax meant to seek an admission related to *Endo Pharmaceuticals Inc. v. Actavis, Inc.*, 746 F.3d 1371 (Fed. Cir. 2014).

Complaint Counsel admits Request No. 11.

Request No. 12: Admit that in May 2011, Johnson Matthey contacted Impax about U.S. patent No. 7,851,482.

Response and Specific Objections to Request No. 12:

Complaint Counsel objects to Request No. 12 on the basis that the phrase "contacted Impax about U.S. patent No. 7,851,482" is vague and ambiguous.

Complaint Counsel cannot truthfully admit or deny Request for Admission No. 12. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny whether Johnson Matthey contacted Impax in May 2011 about U.S. patent No. 7,851,482. An email thread produced by Impax, with bates numbers IMPAX-OPANA-CID00020787-92, indicates that on May 27, 2011 Johnson Matthey contacted Impax about "JM's patent issued in Dec'10 for Oxymorphone" but it is not clear whether this refers to U.S. patent No. 7,851,482, and Complaint Counsel has no additional information about the content of communications between Johnson Matthey and Impax.

Request No. 13: Admit that in May 2011, Johnson Matthey contacted Impax about a possible license to U.S. patent No. 7,851,482.

Response and Specific Objections to Request No. 13:

Complaint Counsel objects to Request No. 13 on the ground that the phrase "about a possible license to U.S. patent No. 7,851,482" is vague and ambiguous.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny. An email thread produced by Impax, with bates numbers IMPAX-OPANA-CID00020787-92, indicates that on May 27, 2011, Johnson Matthey contacted Impax about "JM's patent issued in Dec'10 for Oxymorphone" but it is not clear whether this refers to U.S. patent No. 7,851,482, and no license was mentioned. Complaint Counsel has no additional information about the content of communications between Johnson Matthey and Impax and is not aware of Impax taking any significant steps to get a license to the '482 patent from Johnson Matthey, if Impax had an opportunity to do so prior to Endo's acquisition of a field-of-use license to the patent.

Request No. 14: Admit that after Endo offered, and Impax accepted, the settlement provision that became the Co-Exclusive License Provision, Impax negotiated a license date under the Settlement & License Agreement that was earlier than the license date proposed by Endo on May 26, 2010.

Response and Specific Objections to Request No. 14:

Complaint Counsel objects to Request No. 14 on the basis that the terms "offered" and "accepted" are vague and ambiguous.

Complaint Counsel denies Request No. 14. The terms of the Settlement & License Agreement were not accepted by either party until the entire agreement was fully executed on June 8, 2010.

Request No. 15: Admit that after Endo offered, and Impax accepted, the settlement provision that became the Co-Exclusive License Provision, Impax negotiated a license date under the Settlement & License Agreement that was earlier than the license date proposed by Endo on June 1, 2010.

Response and Specific Objections to Request No. 15:

Complaint Counsel objects to Request No. 15 on the basis that the terms "offered" and "accepted" are vague and ambiguous.

Complaint Counsel denies Request No. 15. The terms of the Settlement & License Agreement were not accepted by either party until the entire agreement was fully executed on June 8, 2010.

Request No. 16: Admit that after Endo and Impax began negotiating the settlement provision that became the Endo Credit Provision, Impax negotiated a license date under the Settlement & License Agreement that was earlier than the license date proposed by Endo on May 26, 2010.

Response and Specific Objections to Request No. 16:

Complaint Counsel objects to Request No. 16 on the basis that the phrase "the settlement provision that became the Endo Credit Provision" is vague and ambiguous. Complaint Counsel further objects that the phrase "negotiated a license date" is vague and ambiguous.

Complaint Counsel admits that on May 26, 2010, Endo provided a term sheet to Impax that included a March 10, 2013 entry date. On May 27, 2010, Impax responded with an email that it said "more closely reflect[ed]" the parties' prior communications. That email proposed a January 1, 2013 entry date "with no authorized generic and certain acceleration triggers, including market degradation to any alternate product." Over the course of the negotiations, Impax and Endo agreed to an entry date of January 1, 2013 with no authorized generic during the first-filer exclusivity period, no acceleration trigger

in the case of market degradation, and the Endo Credit Provision. Complaint Counsel otherwise denies Request No. 16 except as specifically admitted herein.

Request No. 17: Admit that after Endo and Impax began negotiating the settlement provision that became the Endo Credit Provision, Impax negotiated a license date under the Settlement & License Agreement that was earlier than the license date proposed by Endo on June 1, 2010.

Response and Specific Objections to Request No. 17:

Complaint Counsel objects to Request No. 17 on the ground that the phrase "the settlement provision that became the Endo Credit Provision" is vague and ambiguous. Complaint Counsel further objects that the phrase "negotiated a license date" is vague and ambiguous.

Complaint Counsel admits that on June 1, Chris Mengler of Impax reported internally that Endo's "current proposal" included a "Generic launch" date of "February 1, 2013 (with the usual bells and whistles relating to acceleration)." Prior to that proposal, on May 26, 2010, Endo provided a term sheet to Impax that included a March 10, 2013 entry date. On May 27, 2010, Impax responded with an email that it said "more closely reflect[ed]" the parties' prior communications. That email proposed a January 1, 2013 entry date "with no authorized generic and certain acceleration triggers, including market degradation to any alternate product." On June 2, 2010, Mr. Mengler sent an internal email stating "Here is where we are at tonight." The email stated that "we enter jan 1 2013 with no ag." It further stated that "We also get agreement to protect a 50% market share through certain mechanisms." Over the course of negotiations, Impax and Endo agreed to an entry date of January 1, 2013 with no authorized generic during the first-filer exclusivity period, no acceleration trigger for market degradation, and the Endo Credit Provision. Complaint Counsel otherwise denies Request No. 17 except as specifically

admitted herein.

Request No. 18: Admit that at the time Impax and Endo executed the Settlement & License Agreement, it was possible that Impax ultimately could have been required to make a net payment to Endo pursuant to Sections 4.3 and 4.4 of the Settlement & License Agreement.

Response and Specific Objections to Request No. 18:

Complaint Counsel objects to Request No. 18 on the ground that the term "net payment" is vague and ambiguous. Complaint Counsel further objects to this request on the basis that it is a hypothetical, asks Complaint Counsel to speculate, and seeks an admission on an event that did not happen. Complaint Counsel further objects that this Request is not reasonably calculated to yield information relevant to the allegations of the complaint, to the proposed relief, or the defenses of Respondent because it ignores Endo's agreement not to launch an authorized generic under Section 4.1 of the Settlement & License Agreement.

Complaint Counsel denies Request No. 18.

Request No. 19: Admit that at the time Impax and Endo executed the Settlement & License Agreement, neither Impax nor Endo reasonably could have anticipated the Novartis Plant Closure.

Response and Specific Objections to Request No. 19:

Complaint Counsel objects to Request No. 19 on the ground that the phrase "reasonably could have anticipated" is vague and ambiguous. Complaint Counsel further objects to this Request on the basis that it asks Complaint Counsel to speculate.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny. Complaint Counsel has no way to know whether Impax or Endo reasonably could have anticipated the Novartis Plant Closure at the time they executed the Settlement & License Agreement.

Request No. 20: Admit that, at the time Impax and Endo executed the Settlement & License Agreement, neither Impax nor Endo reasonably could have known about the Novartis Plant Closure.

Response and Specific Objections to Request No. 20:

Complaint Counsel objects to Request No. 20 on the ground that the phrase "reasonably could have known" is vague and ambiguous. Complaint Counsel further objects to this Request on the basis that it asks Complaint Counsel to speculate.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny. Complaint Counsel has no way to know whether Impax or Endo reasonably could have known about the Novartis Plant Closure at the time they executed the Settlement & License Agreement.

Request No. 21: Admit that at the time Impax and Endo executed the Settlement & License Agreement, neither Impax nor Endo had any control over the Novartis Plant Closure.

Response and Specific Objections to Request No. 21:

Complaint Counsel objects to Request No. 21 on the ground that the phrase "had any control over" is vague and ambiguous.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny. Complaint Counsel has no way to know whether Impax or Endo had any control over the Novartis Plant Closure.

Request No. 22: Admit that, but for the Novartis Plant Closure, it would have been possible for Endo to introduce a reformulated version of Opana ER before January 1, 2013, without being required to make any payment to Impax under Section 4.4 of the Settlement & License Agreement.

Response and Specific Objections to Request No. 22:

Complaint Counsel objects to Request No. 22 on the ground that the phrase "it would have been possible" is vague and ambiguous. Complaint Counsel further objects to this Request on the ground that it is hypothetical. Complaint Counsel further objects that the Request is not reasonably calculated to yield information relevant to the allegations of the complaint, to the proposed relief, or the defenses of Respondent because it ignores Endo's commitment not to market an authorized generic product under Section 4.1 of the Settlement & License Agreement.

Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny.

Request No. 23: Admit that Impax had no control over whether or when Endo might submit an NDA for a reformulated version of Opana ER.

Response and Specific Objections to Request No. 23:

Complaint Counsel objects to Request No. 23 on the ground that the phrase "had no control over" is vague and ambiguous.

Complaint Counsel admits Request No. 23.

Request No. 24: Admit that Impax had no control over whether or when the FDA might approve an NDA for a reformulated version of Opana ER.

Response and Specific Objections to Request No. 24:

Complaint Counsel objects to Request No. 24 on the ground that the phrase "had no control over" is vague and ambiguous.

Complaint Counsel admits Request No. 24.

Request No. 25: Admit that Impax had no control over whether or when Endo might move original Opana ER to the discontinued drugs list.

Response and Specific Objections to Request No. 25:

Complaint Counsel objects to Request No. 25 on the ground that the phrase "had no control over" is vague and ambiguous.

Complaint Counsel admits Request No. 25.

Request No. 26: Admit that Endo did not report the possibility of a payment under the Endo Credit Provision in any filing with the Securities and Exchange Commission, or in any other required public financial disclosure, until 2012.

Response and Specific Objections to Request No. 26:

Complaint Counsel objects to Request No. 26 on the ground that the term "required public financial disclosure" is vague and ambiguous. Complaint Counsel further objects to this Request on the ground that it requires a legal conclusion about what public financial disclosure forms Endo was required to file.

Complaint Counsel denies Request No. 26. Penwest, which was acquired by Endo, reported the Settlement & License Agreement in its August 6, 2010 Form 10-Q and included a redacted version of the Endo Credit Provision as an attachment to that filing.

Request No. 27: Admit that Impax's Board of Directors did not vote to authorize an at-risk launch of generic original Opana ER.

Response and Specific Objections to Request No. 27:

Complaint Counsel objects to Request No. 27 on the ground that the phrase "did not vote to authorize" is vague and ambiguous.

Complaint Counsel admits that Impax's Board of Directors did not vote either to authorize or not authorize an at-risk launch of generic original Opana ER.

Request No. 28: Admit that Impax has never Launched At Risk without first obtaining authorization from Impax's Board of Directors do so.

Response and Specific Objections to Request No. 28:

Complaint Counsel objects to Request No. 28 on the ground that the phrase "obtaining authorization from Impax's Board of Directors" is vague and ambiguous.

Complaint Counsel admits that Impax stated in an interrogatory response to Complaint Counsel that it had never launched at risk without first obtaining authorization from Impax's Board of Directors to do so. Beyond this, Complaint Counsel cannot truthfully admit or deny the Request. Complaint Counsel has made reasonable inquiry and the information known to or readily obtainable by Complaint Counsel is insufficient to enable it to admit or deny that Impax has never Launched At Risk without first obtaining authorization from Impax's Board of Directors to do so.

Request No. 29: Admit that in *FTC v. Actavis*, 133 S. Ct. 2223 (2013), the United States Supreme Court identified as a relevant metric in the antitrust analysis of "reverse payment settlement agreements" the litigation costs of the payor of the alleged "reverse payment," not the payee.

Response and Specific Objections to Request No. 29:

Complaint Counsel objects to Request No. 29 on the ground that it is an improper Request for Admission and requests a legal interpretation. Complaint Counsel further objects on the ground that the term "relevant metric" is vague and ambiguous.

Complaint Counsel admits that the Supreme Court made the following statements in *FTC v. Actavis*: (1) "Where a reverse payment reflects traditional settlement considerations, such as avoided litigation costs or fair value for services, there is not the same concern that a patentee is using its monopoly profits to avoid the risk of patent invalidation or a finding of noninfringement." (133 S. Ct. at 2236); (2) "[T]he likelihood of a reverse payment bringing about anticompetitive effects depends upon its size, its scale in relation to the payor's anticipated future litigation costs, its independence from other services for which it might represent payment, and the lack of any other convincing

justification." (*id.* at 2237). Complaint Counsel notes that these statements refer specifically to "**avoided** litigation costs" and "**anticipated future** litigation costs." Complaint Counsel otherwise denies Request No. 29 except as specifically admitted herein.

Request No. 30: Admit that in *FTC v. Actavis*, 133 S. Ct. 2223 (2013), the United States Supreme Court identified as relevant to the antitrust analysis of "reverse payment settlement agreements" "potentially offsetting legal considerations present in the circumstances" including "those related to patents."

Response and Specific Objections to Request No. 30:

Complaint Counsel objects to Request No. 30 on the ground that it is an improper Request for Admission and requests a legal interpretation. Complaint Counsel further objects on the ground that the phrase "relevant to the antitrust analysis" is vague and ambiguous.

Complaint Counsel admits that, in summarizing some of its prior antitrust case law, the Supreme Court stated: "In short, rather than measure the length or amount of a restriction solely against the length of the patent's term or its earning potential, as the Court of Appeals apparently did here, this Court answered the antitrust question by considering traditional antitrust factors such as likely anticompetitive effects, redeeming virtues, market power, and potentially offsetting legal considerations present in the circumstances, such as here those related to patents." *FTC v. Actavis*, 133 S. Ct. at 2231. Complaint Counsel otherwise denies Request No. 30 except as specifically admitted herein.

Request No. 31: Admit that in *Board of Trade v. United States*, 246 U.S. 231, 238 (1918), the Supreme Court held that, under the rule of reason "the court must ordinarily consider the facts peculiar to the business to which the restraint is applied; its condition before and after the restraint was imposed; the nature of the restraint and its effect, actual or probable" and that "[t]he history of the restraint, the evil believed to exist, the reason for adopting the particular remedy, the purpose or end sought to be attained, are all relevant facts."

Response and Specific Objections to Request No. 31:

Complaint Counsel objects to Request No. 31 on the ground that it is an improper Request for Admission and requests a legal interpretation.

Complaint Counsel admits that the quoted statements appear in *Board of Trade v. United States*.

Request No. 32: Admit that the Co-Exclusive License Provision was legal under federal antitrust law as it existed at the time Impax and Endo entered into the Settlement & License Agreement.

Response and Specific Objections to Request No. 32:

Complaint Counsel objects to Request No. 32 on the ground that it is an inappropriate Request for Admission and asks for a legal interpretation. Complaint Counsel further objects to this Request on the ground that the phrase "legal under federal antitrust law as it existed at the time Impax and Endo entered into the Settlement & License Agreement" is vague and ambiguous.

Complaint Counsel denies Request No. 32. Federal courts have long held that an agreement between potential competitors not to compete violates the federal antitrust laws and the FTC Act.

Request No. 33: Admit that, at the time Impax and Endo entered into the Settlement & License Agreement and the Distribution & Co-Promotion Agreement, no federal court had concluded that an agreement between a branded pharmaceutical company and generic pharmaceutical company, under which the branded pharmaceutical company agrees not to sell an "authorized generic" version of one of its branded products, violated federal antitrust laws or the FTC Act.

Response and Specific Objections to Request No. 33:

Complaint Counsel objects to Request No. 33 on the ground that it is an improper Request for Admission and asks for a legal interpretation. Complaint Counsel further objects to this Request on the ground that the term "concluded" is vague and ambiguous.

Complaint Counsel denies Request No. 33. Federal courts have long held that an agreement between potential competitors in which one agrees not to compete violates the federal antitrust laws and the FTC Act.

Request No. 34: Admit that the prevailing federal appellate authority regarding antitrust analysis of "reverse payment settlement agreements" as of June 2010 held that such settlements were lawful if their challenged competitive effects remained within the exclusionary scope of the patents subject to the settlement.

Response and Specific Objections to Request No. 34:

Complaint Counsel objects to Request No. 34 on the ground that it is an improper Request for Admission and asks for a legal interpretation. Complaint Counsel further objects to this Request on the ground that the term "prevailing federal appellate authority" is vague and ambiguous.

Complaint Counsel denies Request No. 34.

Request No. 35: Admit that generic pharmaceutical companies rely primarily on automatic substitution laws to sell their products.

Response and Specific Objections to Request No. 35:

Complaint Counsel objects to Request No. 35 as overbroad to the extent that it seeks a generalization about every product sold by every generic pharmaceutical company. Complaint Counsel further objects that the phrase "rely primarily on automatic substation laws to sell their products" is vague and ambiguous.

Complaint Counsel admits that automatic substitution laws aid generic pharmaceutical companies in selling their products, but states that generic pharmaceutical products can also be sold without automatic substitution.

Request No. 36: Admit that state automatic substitution laws typically allow or require automatic substitution of a generic drug product for a prescribed product only where, at a minimum, the United States Food and Drug Administration has determined the prescribed product and the generic product to be bioequivalent.

Response and Specific Objections to Request No. 36:

Complaint Counsel objects to Request No. 36 on the ground that the term "bioequivalent" is vague and ambiguous.

Complaint Counsel admits that state automatic substitution laws typically only allow or require substitution of a generic drug product for a prescribed product only where the United States Food and Drug Administration has determined the prescribed product and the generic product are A-rated therapeutic equivalents.

Request No. 37: Admit that in April 2010, Impax personnel forecasted a potential "Base Case" launch scenario that assumed a March 2013 launch date for all strengths of Oxymorphone ER. (*See* IMPAX-OPANA-CID00014245, IMPAX-OPANA-CID00014246.)

Response and Specific Objections to Request No. 37:

Complaint Counsel objects to Request No. 37 on the ground that the term "personnel" is vague and ambiguous.

Complaint Counsel admits that, in April 2010, Impax employee Joyce De Los Reyes circulated a forecast with a column labeled "Base Case" that showed a March 2013 launch date for oxymorphone ER—though it also included other scenarios with different dates. This forecast was not an oxymorphone ER-specific forecast. Impax personnel prepared many other forecasts in and around April 2010, including forecasts specific to oxymorphone ER, that projected a June 2010 launch date for the majority of strengths of oxymorphone ER.

Request No. 38: Admit that, at various times in 2009 and 2010, Impax personnel forecasted potential launch scenarios that assumed no competition from an authorized generic version of Oxymorphone ER (*e.g.*, IMPAX-OPANA-CID00011907), competition from an authorized generic beginning in the third month following Impax's assumed launch (*e.g.*, IMPAX-OPANA-CID00007068 [Upside Case]), and competition from an authorized generic beginning in the first month following Impax's assumed launch (*e.g.*, IMPAX-OPANA-CID00007068 [Base Case], IMPAX-OPANA-CID00006922).

Response and Specific Objections to Request No. 38:

Complaint Counsel objects to Request No. 37 on the ground that the term "personnel" is vague and ambiguous. Complaint Counsel further objects to this Request on the ground that it is compound.

Complaint Counsel admits that in July 2009, Impax employee Ted Smolenski circulated a "forecast scenario that protects the upside as we assume we get 100% of the market," giving Impax 100% "Generic Market Share" from June to November 2010. (IMPAX-OPANA-CID00011907) Throughout the first half of 2010, Impax personnel forecasted that, if it launched in June 2010, Impax would face competition from an authorized generic by August 2010, but that if Impax waited to launch until July 2011, it would face generic competition in its first month on the market. Complaint Counsel is not aware of any 2010 Impax sales forecast for generic Opana ER prior to entry of the Settlement and License Agreement that did not assume competition from an authorized generic. Complaint Counsel otherwise denies Request No. 38 except as specifically admitted herein. .

Request No. 39: Admit that Complaint Counsel has no reason to believe that Impax will enter into a Paragraph IV settlement in the future that will violate the antitrust laws.

Response and Specific Objections to Request No. 39:

Complaint Counsel denies Request No. 39.

Dated: August 3, 2017

/s/ Charles A. Loughlin
Charles A. Loughlin
FEDERAL TRADE COMMISSION
Bureau of Competition
600 Pennsylvania Ave., NW
Washington, DC 20580
cloughlin@ftc.gov

Counsel Supporting the Complaint

CERTIFICATE OF SERVICE

I hereby certify that on August 3, 2017, I delivered via electronic mail (FTP) a copy of the foregoing documents to:

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Counsel for Respondent Impax Laboratories, Inc.

Dated: August 3, 2017

By: /s/ Nicholas Leefer
Attorney

EXHIBIT N

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home | Modify Search

Search Results for Proprietary Name, Active Ingredient or Application Number: *oxymorphone*

73 records returned

RX OTC DISCN

CSV Excel

Display 100 records per page

Search for text in the table:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	OXYMORPHONE HYDROCHLORIDE	OPANA	N011707	INJECTABLE	INJECTION	1MG/ML		RLD	RS	ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA	N021611	TABLET	ORAL	5MG	AB	RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA	N021611	TABLET	ORAL	10MG	AB	RLD	RS	ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A204459	TABLET	ORAL	5MG	AB			AUROLIFE PHARMA LLC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203601	TABLET	ORAL	5MG	AB			AVANTHI INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A201187	TABLET	ORAL	5MG	AB			EPIC PHARMA LLC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202321	TABLET	ORAL	5MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A091443	TABLET	ORAL	5MG	AB			TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A090964	TABLET	ORAL	5MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A204459	TABLET	ORAL	10MG	AB			AUROLIFE PHARMA LLC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203601	TABLET	ORAL	10MG	AB			AVANTHI INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A201187	TABLET	ORAL	10MG	AB			EPIC PHARMA LLC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202321	TABLET	ORAL	10MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A091443	TABLET	ORAL	10MG	AB			TEVA PHARMACEUTICALS USA INC

RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203601	TABLET	ORAL	10MG	AB			AVANTHI INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A201187	TABLET	ORAL	10MG	AB			EPIC PHARMA LLC
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RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A091443	TABLET	ORAL	10MG	AB			TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A090964	TABLET	ORAL	10MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	5MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	7.5MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	10MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	15MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	20MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	30MG		RLD		ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N201655	TABLET, EXTENDED RELEASE	ORAL	40MG		RLD	RS	ENDO PHARMACEUTICALS INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	5MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	5MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	5MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	5MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	5MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
										ACTAVIS ELIZABETH

RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	7.5MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	10MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	10MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	10MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	10MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	10MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	15MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	15MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	15MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	15MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	15MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	20MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	20MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	20MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	20MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	20MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			IMPAX LABORATORIES INC

	HYDROCHLORIDE	HYDROCHLORIDE		RELEASE						INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	30MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079046	TABLET, EXTENDED RELEASE	ORAL	40MG	AB			ACTAVIS ELIZABETH LLC AN INDIRECT WHOLLY OWNED SUB OF TEVA PHARMACEUTICALS USA INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A079087	TABLET, EXTENDED RELEASE	ORAL	40MG	AB			IMPAX LABORATORIES INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A202946	TABLET, EXTENDED RELEASE	ORAL	40MG	AB			MALLINCKRODT INC
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A203506	TABLET, EXTENDED RELEASE	ORAL	40MG	AB			SUN PHARMACEUTICAL INDUSTRIES LTD
RX	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200822	TABLET, EXTENDED RELEASE	ORAL	40MG	AB			WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA	N011707	INJECTABLE	INJECTION	1.5MG/ML				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	NUMORPHAN	N011738	SUPPOSITORY	RECTAL	5MG				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	5MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	7.5MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	10MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	15MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	20MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	30MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	40MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC

DISCN	HYDROCHLORIDE	OPANA ER	N021610	EXTENDED RELEASE	ORAL	withdrawn for safety or efficacy reasons**				PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	7.5MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	10MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	15MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	20MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	30MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OPANA ER	N021610	TABLET, EXTENDED RELEASE	ORAL	40MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**				ENDO PHARMACEUTICALS INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	5MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	7.5MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	10MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	15MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	20MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	30MG				PAR PHARMACEUTICAL INC
DISCN	OXYMORPHONE HYDROCHLORIDE	OXYMORPHONE HYDROCHLORIDE	A200792	TABLET, EXTENDED RELEASE	ORAL	40MG				PAR PHARMACEUTICAL INC
Mkt. Status	**Active Ingredient**	**Proprietary Name**	**Appl No**	**Dosage Form**	**Route**	**Strength**	**TE Code**	**RLD**	**RS**	**Applicant Holder**

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EXHIBIT O

REDACTED IN ENTIRETY

EXHIBIT P

REDACTED IN ENTIRETY

EXHIBIT Q

REDACTED IN ENTIRETY

EXHIBIT R

REDACTED IN ENTIRETY

EXHIBIT S

REDACTED IN ENTIRETY

EXHIBIT T

REDACTED IN ENTIRETY

EXHIBIT U

REDACTED IN ENTIRETY

EXHIBIT V

REDACTED IN ENTIRETY

EXHIBIT W

REDACTED IN ENTIRETY

EXHIBIT X

REDACTED IN ENTIRETY

EXHIBIT Y

REDACTED IN ENTIRETY

EXHIBIT Z

REDACTED IN ENTIRETY

EXHIBIT AA

REDACTED IN ENTIRETY

EXHIBIT BB

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

ENDO PHARMACEUTICALS INC.,

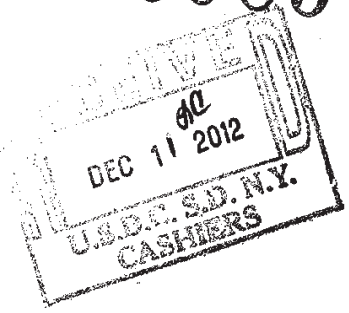
Plaintiff,

v.

ACTAVIS INC. and
ACTAVIS SOUTH ATLANTIC LLC,

Defendants.

C.A. No. 12 CV 8985



COMPLAINT

Plaintiff Endo Pharmaceuticals Inc. ("Endo") for its Complaint against Defendants Actavis Inc. and Actavis South Atlantic LLC (collectively "Defendants"), allege as follows:

PARTIES

1. Plaintiff Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceuticals company engaged in the research, development, sale and marketing of prescription pharmaceuticals used, among other things, to treat and manage pain. Endo markets and distributes OPANA® ER, an innovative opioid painkiller designed to be crush-resistant (alternatively referred to herein as "Opana ER CRF")

2. Upon information and belief, defendant Actavis Inc. is a corporation organized and existing under the laws of the State of Delaware, having its headquarters and principal place of business at 60 Columbia Road, Building B, Morristown, New Jersey 07960. Actavis Inc. is a pharmaceutical company engaged in the development, manufacture, sale and marketing of generic pharmaceuticals for sale and use throughout the United States, including in this judicial

district.

3. Upon information and belief, Actavis South Atlantic LLC ("ASA") is a limited liability company, organized and existing under the laws of the State of Delaware, having its principal place of business at 13800 N.W. 2nd Street, Suite 190, Sunrise, Florida 33325. ASA is a pharmaceutical company engaged in the development, manufacture, sale and marketing of generic pharmaceuticals for sale and use throughout the United States, including in this judicial district.

4. Upon information and belief, Actavis Inc. controls and directs the operations of ASA, and ASA and Actavis Inc. have acted as each other's alter ego, agent, and partner in the development, manufacturing, distribution, offer for sale, and sale in this judicial district of the infringing product at issue — generic, non crush-resistant "Oxymorphone Hydrochloride Extended-Release Tablets CII" ("Actavis Generic Oxymorphone ER Tablets").

NATURE OF ACTION

5. This is an action arising under the Patent Laws of the United States, 35 U.S.C. § 100, *et seq*.

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a) (patent infringement), and 28 U.S.C. §§ 2201 and 2202 (declaratory judgment).

7. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and 1400(b).

8. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, they have committed — or aided, abetted, planned, contributed to, or participated in the commission of — tortious conduct which will lead to foreseeable harm and

injury to Plaintiff in the State of New York. A substantial part of the events giving rise to Plaintiff's claims occurred in this judicial district. The infringing product at issue is being sold in this judicial district.

9. Defendants maintain continuous and systematic contacts with the State of New York and this District. Defendants market and sell pharmaceutical products through the United States, including the State of New York, and regularly, systematically, and currently transact business in the Southern District of New York, at least by making and shipping into this judicial district, or by offering to sell or selling, or causing others to offer to sell or sell, pharmaceutical products. Defendants derive substantial revenue from goods used or consumed or services rendered in this judicial district.

10. Upon information and belief, Defendants currently sell significant quantities of over forty (40) different generic drug products in the Southern District of New York. Those products include, for example, generic versions of Wellbutrin XL®, Xanax®, and Cardizem® CD. A list of generic products manufactured and sold by Defendants in the United States is provided by Actavis at http://www.actavis.us/en/products/new.htm.

11. Based on the facts and causes alleged herein, and for additional reasons to be developed through discovery, this Court has personal jurisdiction over the Defendants.

FACTUAL BACKGROUND

Endo's Opana ER CRF NDA

12. On December 12, 2011, FDA approved Endo's Supplemental New Drug Application ("sNDA") 201655, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for Opana ER CRF, which is designed to be a crush-resistant tablet that contains oxymorphone hydrochloride for the relief of pain.

13. Opana ER CRF is distributed and sold throughout the United States for relief of moderate to severe pain in patients requiring continuous around-the-clock opioid treatment for an extended period of time.

THE PATENTS

14. On December 14, 2010, the PTO duly and legally issued U.S. Patent No. 7,851,482 (the '482 Patent), entitled "Method For Making Analgesics" to Johnson Matthey Public Limited Company ("Johnson Matthey") as assignee. Jen-Sen Dung, Erno M. Keskeny, and James J. Mencel are named as inventors. A true and correct copy of the '482 Patent is attached as Exhibit A.

15. Endo has acquired full title to the '482 Patent, and is now the sole owner and assignee of the '482 Patent.

16. Information regarding the Endo '482 Patent was submitted to FDA for listing in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2). Pursuant to 21 C.F.R. § 314.53(e), FDA has listed the '482 Patent in the Orange Book with reference to NDA 201655.

17. On November 13, 2012, the PTO duly and legally issued U.S. Patent No. 8,309,122 (the '122 Patent), entitled "Oxymorphone Controlled Release Formulations" to Endo Pharmaceuticals, Inc. as assignee. Huai-Hung Kao, Anand R. Baichwal, Troy McCall, and David Lee are named as inventors. A true and correct copy of the '122 Patent is attached as Exhibit B.

18. Endo is the sole owner and assignee of the '122 Patent.

19. Information regarding the Endo '122 Patent has been submitted to FDA for listing in the Orange Book.

20. On December 11, 2012, the PTO duly and legally issued U.S. Patent No. 8,329,216 (the '216 Patent), entitled "Oxymorphone Controlled Release Formulations" to Endo Pharmaceuticals, Inc. as assignee. Huai-Hung Kao, Anand R. Baichwal, Troy McCall, and David Lee are named as inventors. A true and correct copy of the '216 Patent is attached as Exhibit C.

21. Endo is the sole owner and assignee of the '216 Patent.

22. Information regarding the Endo '216 Patent has been submitted to FDA for listing in the Orange Book.

23. Opana ER CRF is covered by one or more claims of each of the '482, '122 and '216 Patents.

DEFENDANTS' INFRINGING PRODUCT

24. On or about February 2008, ASA filed Abbreviated New Drug Application ("ANDA") No. 79-046 seeking approval to engage in the commercial manufacturing, use and sale of the Actavis's Generic Oxymorphone ER Tablets as a generic version of the original, non-crush-resistant formulation of Opana® ER (the "Discontinued Formulation").

25. In response, Endo filed suit against ASA for infringement of U.S. Patent No. 5,958,456 ("'456 patent"). *See Endo Pharmaceuticals Inc., et. al v. Actavis South Atlantic LLC*, United States District Court, District of New Jersey, Dkt. Nos. 2:08-cv-03482-KSH-PS and 2:08-cv-01563-KSH-PS. Endo and ASA settled their infringement dispute in February 2009.

26. Although the parties' settlement agreement granted Actavis a license under the '456 patent to make and sell its Generic Oxymorphone ER Tablets, nothing in the agreement grants Defendants any license or other rights under the '482, '122 or '216 Patents.

27. Defendants currently make and sell 7.5 mg and 15 mg strengths of the Actavis's

Generic Oxymorphone ER Tablets.

28. Defendants' manufacture and sale of the Actavis Generic Oxymorphone ER Tablets has caused Endo to suffer harm, including without limitation, irreparable injury to its business reputation and goodwill, lost sales of Opana® ER CRF, the loss of the benefit of its investment in developing the reformulated crush-resistant version of Opana® ER, and price erosion for Opana® ER CRF.

COUNT I: INFRINGEMENT OF THE '482 PATENT

29. Endo incorporates each of paragraphs 1-28 above as if set forth fully herein.

30. Defendants' commercial manufacture, sale, and offer for sale of the Actavis Generic Oxymorphone ER Tablets constitutes an infringement of the '482 Patent under 35 U.S.C. § 271(a)-(c).

31. Upon information and belief, Defendants are aware of the existence of the '482 Patent, and are aware that the commercial manufacture, sale, and offer for sale of filing of the Actavis Generic Oxymorphone ER Tablets constitutes infringement of the '482 Patent. Defendants' infringement is willful.

COUNT II: INFRINGEMENT OF THE '122 PATENT

32. Plaintiffs incorporate each of paragraphs 1-31 above as if set forth fully herein.

33. Defendants' commercial manufacture, sale, and offer for sale of the Actavis Generic Oxymorphone ER Tablets constitutes an infringement of the '122 Patent under 35 U.S.C. § 271(a)-(c).

34. Upon information and belief, Defendants are aware of the existence of the '122 Patent, and are aware that the commercial manufacture, sale, and offer for sale of filing of the Actavis Generic Oxymorphone ER Tablets constitutes infringement of the '122 Patent.

Defendants' infringement is willful.

COUNT III: INFRINGEMENT OF THE '216 PATENT

35. Endo incorporates each of paragraphs 1-34 above as if set forth fully herein.

36. Defendants' commercial manufacture, sale, and offer for sale of the Actavis Generic Oxymorphone ER Tablets constitutes an infringement of the '216 Patent under 35 U.S.C. § 271(a)-(c).

37. Upon information and belief, Defendants were aware of the pending issuance of the '216 Patent, and were aware that the commercial manufacture, sale, and offer for sale of filing of the Actavis Generic Oxymorphone ER Tablets would constitute infringement of the patent upon the '216 Patent's issuance. Defendants' infringement is willful.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Endo respectfully requests the following relief:

A. A judgment that Defendants have infringed and are infringing the '482 Patent;

B. A judgment that Defendants have infringed and are infringing the '122 Patent;

C. A judgment that Defendants have infringed and are infringing the '216 Patent;

D. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringement of the '482, '122, and '216 Patents, for the full terms thereof, including any extensions;

E. An order that damages or other monetary relief be awarded to Endo because of Defendants' engaging in the commercial manufacture, use, offer to sell, sale, distribution or importation of the Actavis Generic Oxymorphone ER Tablets, or in inducing such conduct by others, prior to the expiration of the '482, '122, and '216 Patents, and any additional period of

exclusivity to which Plaintiffs are or become entitled, and that any such damages or monetary relief be trebled and awarded to Endo with prejudgment interest;

F. A declaration that this an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

G. Reasonable attorneys' fees, filing fees, and reasonable costs of suit incurred by Endo in this action; and

H. Such other and further relief as the Court may deem just and proper.

Dated: December 11, 2012

By: _____

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Exhibit A

US007851482B2

(12) **United States Patent**
Dung et al.

(10) **Patent No.: US 7,851,482 B2**
(45) **Date of Patent: Dec. 14, 2010**

(54) **METHOD FOR MAKING ANALGESICS**

(75) Inventors: **Jen-Sen Dung**, Boothwyn, PA (US); **Erno M. Keskeny**, Wilmington, DE (US); **James J. Mencel**, North Wales, PA (US)

(73) Assignee: **Johnson Matthey Public Limited Compnay**, London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 646 days.

(21) Appl. No.: **11/866,840**

(22) Filed: **Oct. 3, 2007**

(65) **Prior Publication Data**

US 2008/0146601 A1 Jun. 19, 2008

(30) **Foreign Application Priority Data**

Dec. 14, 2006 (GB) 0624880.1

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/04 (2006.01)

(52) **U.S. Cl.** **514/282**; 546/45; 546/44

(58) **Field of Classification Search** 514/282; 546/45, 44

See application file for complete search history.

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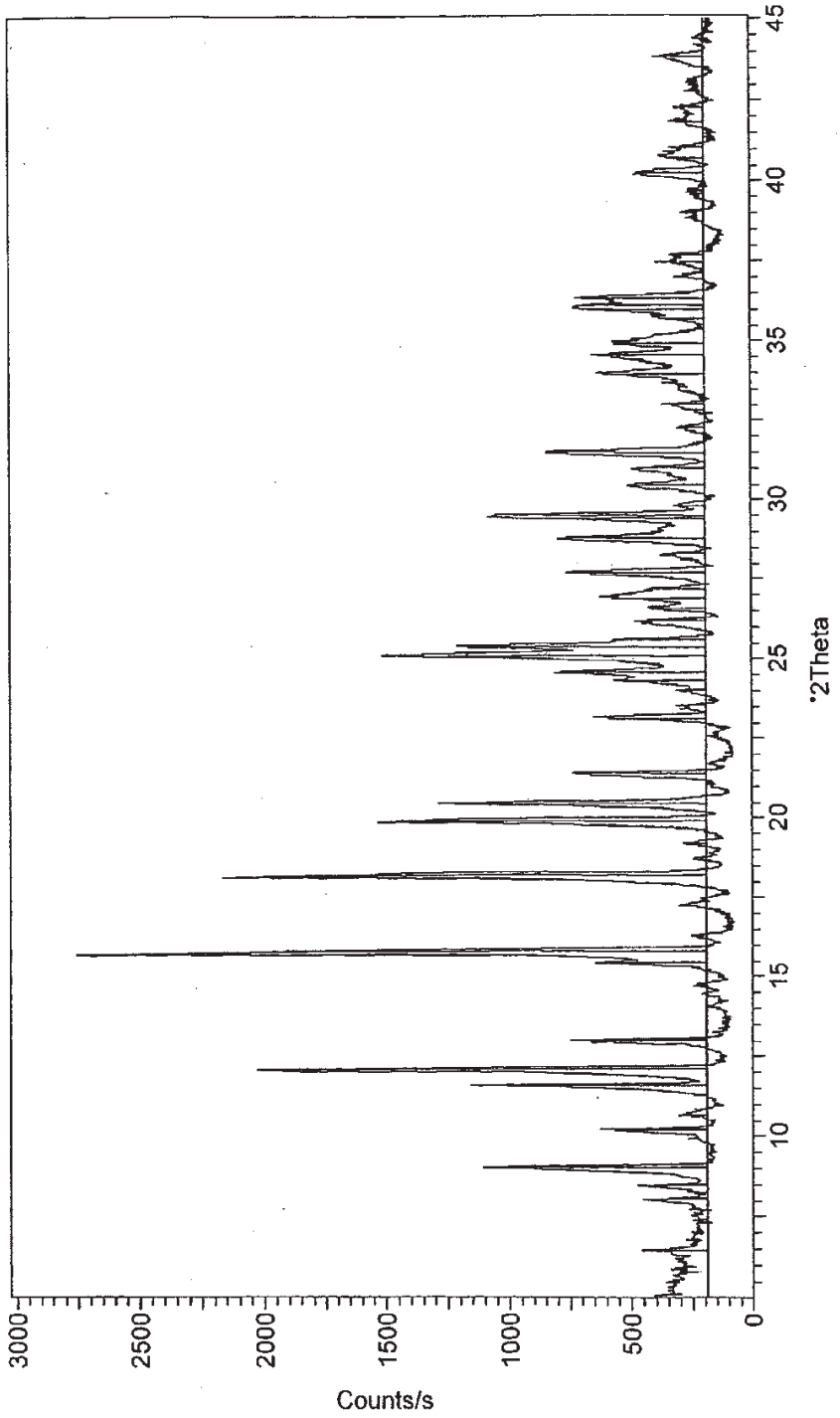
Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—RatnerPrestia

(57) **ABSTRACT**

Improved analgesic oxymorphone hydrochloride contains less than 10 ppm of alpha, beta unsaturated ketones and pharmaceutical preparations comprising such oxymorphone hydrochloride. The oxymorphone hydrochloride is produced by reducing a starting material oxymorphone hydrochloride using gaseous hydrogen and under specified acidity, solvent system and temperature conditions. A specific polymorph of oxymorphone hydrochloride may be obtained by hydration.

21 Claims, 1 Drawing Sheet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METHOD FOR MAKING ANALGESICS

FIELD OF THE INVENTION

This invention concerns an improved method for making analgesics, more especially for making the opiate oxymorphone as its hydrochloride.

BACKGROUND OF THE INVENTION

Oxymorphone, generally administered in the form of its hydrochloride salt, is a potent semi-synthetic opiate analgesic, for the relief of moderate to severe pain, and has been approved for use since 1959. It can be administered as an injectable solution, suppository, tablet or extended release tablet. It is desirable to develop high purity forms of oxymorphone and a method for its synthesis.

Several methods for synthesising oxymorphone from compounds isolated from the opium poppy or compounds derived therefrom are known, for example, starting from morphine, thebaine, or from oxycodone. There remains the need for methods which permit the formation of oxymorphone with low contamination of alpha, beta unsaturated ketones. The present invention provides an improved oxymorphone product and a method for producing such oxymorphone.

U.S. Pat. No. 7,129,248 claims a process for producing oxycodone hydrochloride with less than 25 ppm of 14-hydroxycodeinone, by hydrogenating oxycodone having greater than 100 ppm 14-hydroxycodeinone. The synthetic route to oxycodone taught in US'248 starts from thebaine and produces 14-hydroxycodeinone as an intermediate product and 8,14-dihydroxy-7,8-dihydrocodeinone as a by-product resulting from over-oxidation of thebaine. During conversion of oxycodone free base to the hydrogen chloride salt, the by-product may undergo acid-catalysed dehydration and be converted into 14-hydroxycodeinone. Thus the final oxycodone hydrogen chloride salt contains unreacted 14-hydroxycodeinone as well as 14-hydroxycodeinone derived from the by-product 8,14-dihydroxy-7,8-dihydrocodeinone. A hydrogenation step is claimed to reduce contents of 14-hydroxycodeinone from at least 100 ppm to less than 25 ppm.

SUMMARY OF THE INVENTION

The present invention provides an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones.

The invention also provides a method of purifying oxymorphone hydrochloride to yield an oxymorphone hydrochloride product containing less than 10 ppm of alpha, beta unsaturated ketones, which method comprises reducing a starting material oxymorphone hydrochloride in a strongly acid water and alcohol solvent, using gaseous hydrogen at a temperature in the range from 60 to 70° C. Reduction is suitably carried out for a period of at least 20 hours, but in another embodiment, reduction is carried out for 1 to 20 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described below with reference to the drawing, in which:

FIG. 1 is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

DETAILED DESCRIPTION OF THE INVENTION

Preferably, the solvent is ethanol/water, although other water miscible alcohols, such as isopropanol and n-propanol, may be used. The reaction medium is very acidic, preferably by incorporating at least two equivalents of hydrochloric acid. A pH of less than 1 is desirable.

The reaction temperature is most preferably maintained at about 65° C. Hydrogen is conveniently supplied to the reaction vessel at 2.41 bar pressure.

The method of the invention has been able to reduce starting material oxymorphone hydrochloride having very high (of the order of 0.3 to 0.5%, or 3,000 to 5,000 ppm) content of alpha, beta unsaturated ketones to less than 10 ppm, and in many cases to undetectable levels (by HPLC).

The starting material oxymorphone hydrochloride may be an isolated or non-isolated material. Desirably, it has been obtained by the formation of the hydrogen chloride salt by heating oxymorphone free base in the presence of hydrochloric acid and an alcohol/water reaction medium. Suitable temperatures are 60-70° C. It can be seen that the reaction medium is ideal for the reduction of the method of the invention, so that it is generally not necessary to isolate the oxymorphone hydrochloride. However, the starting material oxymorphone hydrochloride may be isolated from the reaction medium or may be from another source.

The oxymorphone free base is itself preferably prepared by a reduction of 14-hydroxymorphinone. This may be carried out in a single- or two-stage process. The reduction is preferably carried out in acetic acid using gaseous hydrogen and a palladium on carbon catalyst. Preferred temperatures are of the order of 30° C. The base is precipitated by adding aqueous ammonia (NH_4OH).

This reduction may be in the presence of the reaction medium to which is added dichloromethane in methanol, Florasil and n-propanol.

The 14-hydroxymorphinone itself is most suitably prepared by hydroxylation of oripavine, using hydrogen peroxide in the presence of formic acid.

Oripavine is a known compound, which is extractable from poppy straw. The strain developed in Tasmania to be a high-Thebaine-yielding strain also produces higher than normal levels of oripavine.

The process of the invention is highly flexible, permitting many reaction steps to be carried out without isolation of intermediate products, whilst still retaining high (of the order of 50%) overall yields from oripavine, as well as remarkably high purity. Under favourable conditions, the presence of alpha, beta unsaturated ketones is undetectable by conventional means such as HPLC, but the skilled person can readily achieve less than 10 ppm contamination. The process of the invention has been successfully carried out at kilogram scale.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active component. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, colouring, flavouring and/or aro-

matic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, solutions, suspensions, etc.

In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described herein.

When the dosage form is oral, the dosage form of the present invention contains from about 1 mg to about 40 mg of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Particularly preferred dosages are about 5 mg, about 10 mg, about 20 mg or about 40 mg however other dosages may be used as well. The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release of having less than 10 ppm of alpha, beta unsaturated ketones. Such formulations can be prepared in accordance with US 2003/129230 A1, US 2003/129234 A1 and US 2003/157167 A1.

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material that is incorporated into a matrix along with the oxymorphone salt thereof.

The sustained release dosage form may optionally comprise particles containing oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, and a plurality of the resultant solid sustained release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The sustained release bead formulations of the present invention slowly release the active component of the present invention, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticiser is added to the hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with the agent(s) of the present are prepared, e.g., by dissolving the agent(s) in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active to the beads, and/or to color the solution, etc. For example, a product that includes hydroxypropylmethylcellulose, etc with or without colorant (e.g., Opadry™, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in these example beads, may then be optionally overcoated with a barrier agent, to separate the active component(s) from the hydrophobic sustained release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticiser, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticiser. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticiser, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Colour may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, colour may be added to Aquacoat™ via the use of alcohol or propylene glycol based colour dispersions, milled aluminium lakes and opacifiers such as titanium dioxide by adding colour with shear to water soluble polymer solution and then using low shear to the plasticised Aquacoat™. Alternatively, any suitable method of providing colour to the formulations of the present invention may be used. Suitable ingredients for providing colour to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and colour pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticised hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidised-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic

material, a further overcoat of a film-former, such as Opadry™, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the agent(s) from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents, which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semipermeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864.

Matrix Formulations

In other embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a sustained release coating as set forth herein. The materials suitable for inclusion in a sustained release matrix may depend on the method used to form the matrix.

For example, a matrix in addition to the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may include: hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. The list is not meant to be exclusive, any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit™. RSPO—the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° C. and 90° C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly (methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 25° C. to about 200° C., preferably from about 45° C. to about 90° C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For the purposes of the present invention, a wax-like substance is defined as any material that is normally solid at room temperature and has a melting point of from about 25° C. to about 100° C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° C. and 90° C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropyl-methylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxymorphone hydrochloride release required. The at least

one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioidoxycmorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a (w/w) of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

Matrix—Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} to C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxalkyl cellulose granules with water.

In yet other alternative embodiments, a spheronizing agent, together with the active component can be spheronized to form spheroids. Microcrystalline cellulose is a preferred spheronizing agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropyl-cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 mm to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 hours to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, the oxymorphone hydrochloride

having less than 10 ppm of alpha, beta unsaturated ketones, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For the purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 mm to about 12 mm in length and have a diameter of from about 0.1 mm to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tabletting equipment using standard techniques. Techniques and compositions for making tablets (compressed and moulded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681, described in additional detail above.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule containing the multiparticulates can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2% to about 30%, although the overcoat may be greater depending upon the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded particles before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release agent for prompt release. The immediate release agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., sustained release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of sustained release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the agent(s), e.g. when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the active in desired areas of the gastrointestinal (GI) tract, e.g. the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2% to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail U.S. Pat. No. 5,273,760, U.S. Pat. No. 5,286,493, U.S. Pat. No. 5,324,351, U.S. Pat. No. 5,356,467, and U.S. Pat. No. 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose,

although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described as fully polymerised copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings, which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™ from Rohm Tech, Inc. There are several different types of Eudragit™, for example Eudragit™ E is an example of a methacrylic acid copolymer that swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, or 10% Eudragit™ RL and 90% Eudragit™ RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticiser in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticiser into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticiser included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 wt % to about 50 wt % of the film-former. Concentration of the plasticiser, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

The addition of a small amount of talc may also help reduce the tendency of the aqueous dispersion to stick during processing, and may act as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones can be pumped, diffuse or migrate through a fibre, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be

formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. No. 3,845,770, U.S. Pat. No. 3,916,899, U.S. Pat. No. 4,063,064 and U.S. Pat. No. 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. No. 4,200,098 and U.S. Pat. No. 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_nH_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethyl-cellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as an osmogel), whereby they push the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulphate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulphate, sodium sulphate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkyl-cellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a non-toxic colorant or dye. Examples of colourants or dyes include but are not limited to Food and Drug Administration Colourants (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation, semipermeable crosslinked polystyrenes, semipermeable crosslinked poly(sodium styrene sulfonate), semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride) and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present

invention are known in the art including those in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones equivalent to 10 to 40 mg oxymorphone hydrochloride, 25 mg to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 mg to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 mg to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones. Preparation of sustained release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the suppository base, or the melting of the base and subsequent partition of the drug from the suppository base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular suppository base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factors affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionisation, and lipid solubility.

The suppository base chosen should be compatible with the active of the present invention. Further, the suppository base is preferably non-toxic and non-irritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol™ (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20% to about 90% by weight of the total weight of the suppository. Preferably, the amount of suppository base in the suppository is from about 65% to about 80%, by weight of the total weight of the suppository.

Additional Embodiments

The oxymorphone hydrochloride having less than 10 ppm of alpha, beta unsaturated ketones may be used as a substitute for the oxymorphone hydrochloride in any existing commercial product such as, e.g., Opana™, Opana ER™ and Numorphan™. Such formulations are listed in the FDA Orange Book.

EXAMPLES

The invention will now be illustrated by the following examples, showing the synthesis of the high purity oxymorphone, starting from oripavine.

FIG. 1 is the Powder X-Ray Diffraction pattern collected for a hydrated oxymorphone hydrochloride product made according to Example 3.2D.

Example 1.1A

Hydroxylation of Oripavine to 14-hydroxymorphinone

1 kg oripavine is added with stirring to a reaction vessel containing 2.76 kg of formic acid and 0.53 kg water, and stirring is continued until the oripavine is completely dissolved, and the temperature remains in the range 20-30° C. Subsequently, 0.36 kg of 35 wt % hydrogen peroxide solution

is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction vessel is cooled to 10° C. and 7.12 litres of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 40° C. If necessary, the pH of the reaction mixture is adjusted to the range 8 to 10, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 3-5 hours.

A precipitate of product 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water until colourless and then dried to a damp cake and collected for the next stage.

Example 1.1B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with kg litre water and 0.73 kg acetic acid before adding 1 kg of 14-hydroxymorphinone prepared as in Example 1.1A and the mixture stirred until clear. 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen, and hydrogen supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, the pH of the filtrate is adjusted to pH 9 using ammonium hydroxide solution, the product precipitates and is isolated by filtration and dried under vacuum. The product is dissolved in dichloromethane/methanol (9:1 v/v) and slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 66% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.51% by area measurement.

Example 1.1C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 1 kg of oxymorphone base, prepared as in Example 1.1B, together with 2.05 kg of absolute alcohol and 0.66 kg of water. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 0.66 kg concentrated hydrochloric acid, 0.24 kg of water and 0.31 kg of absolute alcohol is added to the oxymorphone base slurry and the pH checked to ensure that it is <1.0. 40 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through Celite and a 0.2 μm polish filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is washed with absolute alcohol then dried. Yield is 80%.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 6.2 ppm.

Example 1.2A

Hydroxylation of Oripavine to 14-hydroxymorphinone

40 g of Oripavine is added with stirring to a reaction vessel containing 30 g of water and 85 g of formic acid, and stirring continued until oripavine is completely dissolved. The temperature remains in the range 20-30° C. Subsequently, 17.72 g of 30 wt % hydrogen peroxide solution is added, and the reaction mixture is stirred for three hours or more, whilst maintaining the temperature in the range 20-35° C. The reaction mixture is cooled to <20° C. and 335 mL of dilute ammonium hydroxide is added slowly, whilst maintaining the reaction mixture below 32° C. If necessary, the pH of the reaction mixture is adjusted to 9.0, with more dilute ammonium hydroxide solution or hydrochloric acid as appropriate, and stirring is continued for 2 hours at 20 C and 2 hours at 4-5° C.

A precipitate of 14-hydroxymorphinone is formed and filtered off. The precipitate is washed with water and then dried to a damp cake and collected for the next stage.

Example 1.2B

Formation of Oxymorphone Base

A hydrogenation vessel is charged with 148 g of water, 90.6 g of acetic acid, and 250 g of damp 14-hydroxymorphinone (48% water content), prepared as in Example 1.2A. The mixture is stirred until clear then 1.34 g of 10% Pd on carbon catalyst (dry weight) in the form of a paste is added under a stream of nitrogen. The hydrogenation vessel is flushed with nitrogen and hydrogen respectively, and then the reaction mixture is hydrogenated at 30° C. and 35 psi (2.41 bar) for 5 hours. An in process test by HPLC indicates an 14-hydroxymorphinone area of 0.07%.

Once it is assessed that the reaction is complete, the catalyst is filtered off through a pad of celite, and the celite cake is washed with 25 mL water. The filtrate is cooled to 0-5° C. and the pH is adjusted to 9.5±0.5 with 1:1 mixture (V/V) of concentrated ammonium hydroxide and water. The precipitate is stirred at 0-5° C. for one hour and isolated by filtration. The crude product is dried in vacuum oven at 50° C. to afford 113 g (86.9% yield) of light beige solid. A sample of product is tested by HPLC for alpha, beta unsaturated ketone, and is found to contain 0.27% by area measurement.

113 g of crude oxymorphone base is taken up in 1.13 L of dichloromethane/methanol (9:1, v/v). 113 g of florisil is added to the solution and the mixture is stirred for 12 hours. The mixture is filtered through a pad of 113 g of florisil, and the florisil cake is rinsed with 120 mL of dichloromethane/methanol. The solvent is removed by distillation and then switched to n-propanol. The batch is cooled to 0-5° C. and stirred for 1 hour to precipitate the oxymorphone base, which is filtered off, washed with cold n-propanol, and dried in a vacuum oven to afford 67.2 g (59.47%) of white solids.

A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.027% by area measurement.

Example 1.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 50.1 g of oxymorphone base, prepared as in Example 1.2B, together with 120 g of absolute alcohol. The mixture is heated to 60±2° C. and stirred to form a slurry. A hydrochloric acid solution prepared from 32.7 g concentrated hydrochloric acid and 33.6 g of water is added to the oxymorphone base slurry and the pH is checked to ensure that it is <1.0. 2.0 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65° C. The reaction mixture is filtered whilst hot through Celite. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with absolute alcohol and then dried to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 1.1 ppm.

The above method may be varied by the skilled person whilst still maintaining excellent purity of the product oxymorphone hydrochloride, and examples of such variations follow.

Example 2.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 2.5 kg of water and 0.73 kg of acetic acid and 1 kg of 14-hydroxymorphinone is added to the vessel. The reaction mixture is stirred until a clear solution is obtained before 40 g of wet 10% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 3-4 hours. The reaction vessel is cooled to less than 25° C. and a sample subjected to HPLC to check for 14-hydroxymorphinone. If the 14-hydroxymorphinone area detected by HPLC is >0.1%, the hydrogenation is repeated.

Once it is assessed that the reaction is complete, the catalyst is filtered off, dichloromethane/methanol (9:1 v/v) is added to the filtrate and the mixture is adjusted to pH 9-10 by adding ammonium hydroxide solution. The dichloromethane/methanol phase is separate, slurried in florisil, filtered, and the filtrate is distilled to exchange to n-propanol. The n-propanol mixture is cooled and the product precipitates and is collected by filtration in 73% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2B

Reduction of 14-hydroxymorphinone to Oxymorphone Base

A hydrogenation vessel is charged with 35 g of water, 17 g of acetic acid and 38.08 g of 14-hydroxymorphinone, prepared in Example 1.2A. The reaction mixture is stirred until a clear solution is obtained before 1.8 g of wet 5% Pd on carbon catalyst is added under a stream of nitrogen. Hydrogen is supplied at 35-40 psi (2.41-2.76 bar). The temperature is maintained at 30±5° C. until hydrogen uptake stops, then the vessel is maintained at 35-40 psi (2.41-2.76 bar) and 30±5° C. for 4 hours. The reaction vessel is cooled to less than 25° C., and a sample is analyzed by HPLC to check for 14-hydroxymorphinone. The 14-hydroxymorphinone area detected by HPLC is 0.26%.

Once it is assessed that the reaction is complete, the catalyst is filtered off and the cake is washed with 15 mL of water. 180 mL of dichloromethane/methanol (9:1, v/v) are added to the filtrate and the pH of the mixture is adjusted to pH 9-10 by adding concentrated ammonium hydroxide. The dichloromethane/methanol layer is separated and purified by slurrying with ca. 20 g florisil. The slurry is filtered and the filtrate is distilled to exchange into n-propanol, and the mixture is cooled to 0-5° C. and stirred for 1-2 hours to precipitate oxymorphone base, which is isolated by filtration. The oxymorphone base is then slurried from n-propanol providing product in 74% yield. A sample of product is tested by HPLC for alpha, beta unsaturated ketones, and is found to contain 0.32% by area.

Example 2.2C

Formation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 2.5 g of oxymorphone base, prepared as in Example 2.2B, together with 7.5 mL of absolute alcohol, 2.5 g of water and 1.66 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.111 g of 10% Pd on carbon catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 21 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form oxymorphone hydrochloride as a precipitate. The precipitate is filtered off, washed with cold absolute alcohol and dried under vacuum to afford white crystals in 77% yield.

A sample of the product is tested by HPLC for the presence of alpha, beta unsaturated ketones, and is found to contain 2.8 ppm.

Example 3.1B

Reduction of 14-hydroxymorphinone to Oxymorphone Hydrochloride

The procedure for forming the oxymorphinone free base is followed as shown above, but instead of isolating the free base from a dichloromethane/methanol solution, 0.35 volume equivalents of 3N hydrochloric acid are added (vs the volume of the dichloromethane/methanol solution), the reaction mixture is stirred, allowed to stand, and the aqueous layer (contains the product) is separated from the organic layer. The aqueous layer is distilled under vacuum to remove ca. 50% of the volume, and then the remaining solution is cooled over 2 hour to 20-25° C., stirred for 1-2 hours, cooled to 0-5° C. and stirred 2-3 hours. The white solids that form during stirring are filtered off and washed with cold isopropanol. The yield is 64% and the product contains 0.34% of alpha, beta unsaturated ketones.

Example 3.1C

Purification of Oxymorphone Hydrochloride

Using an analogous process to Example 1.1C, but starting from the product of Example 3.1B, purified oxymorphone hydrochloride is obtained in a yield of 92% and having an undetectable content of alpha, beta unsaturated ketones.

Example 3.2C

Preparation of Highly Pure Oxymorphone Hydrochloride

A reaction vessel is charged with 5.05 g of oxymorphone hydrochloride, prepared in Example 3.1B, together with 13.5 mL of absolute alcohol, 4.5 mL of water and 1.51 g of concentrated hydrochloric acid. The mixture is heated to 50-60° C. and a solution results. The pH is checked to ensure that it is <1.0. 0.21 g of 10% Pd on charcoal catalyst water-wet paste is added under a stream of nitrogen to the reaction mixture and the mixture is hydrogenated at 35±5 psi (2.41 bar) for 20 hours whilst maintaining a temperature of 65±3° C. The reaction mixture is filtered whilst hot through a 0.45 μm filter. The filtrate is cooled to 0-5° C. over 2-3 hours, and stirred for a further 2 hours to form a precipitate. The precipitate is collected by filtration, washed with cold absolute alcohol then dried. Yield is 92%.

A sample of the product is tested by HPLC and found to have an undetectable content of alpha, beta unsaturated ketones.

Without changing the basic process steps, but with small variations in the process steps for starting materials, such as isolation or not of such starting materials, and utilising the essential reduction requirements of the invention for the final step to the purified oxymorphone hydrochloride, other products have been obtained with levels of alpha, beta unsaturated ketones of 3.8 ppm, 1.7 ppm, 6.2 ppm, 6.9 ppm, 2.8 ppm, 3.1 ppm, 0.9 ppm, 6.0 ppm and another undetectable, or zero.

Example 3.2D

Hydration of Oxymorphone Hydrochloride

A drying dish is charged with oxymorphone hydrochloride, prepared as in Example 1.1C, 1.2C, 2.2C, 3.1C or 3.2C, which contains about 5-13 wt % of ethanol. The sample is placed in a vacuum oven along with a dish containing 100 mL of water. A vacuum is applied at 24-29 in Hg and the oven maintained at 20-40° C. for 24 hours. An ethanol-free or low ethanol (approx. 0.04 wt %) product is afforded containing about 10-13 wt % of water. The water absorbed by the sample may be removed in a vacuum oven at 50-55° C. The drying process is stopped when the product's KF is 6-8 wt %. The final hydrated oxymorphone hydrochloride affords a uniform polymorph with a consistent X-ray diffraction pattern.

What is claimed:

1. Oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone.

2. Oxymorphone hydrochloride according to claim 1, wherein the content of 14-hydroxymorphinone is less than 5 ppm.

3. A pharmaceutical formulation comprising at least one pharmaceutically acceptable excipient and the oxymorphone hydrochloride according to claim 1.

4. A method of treating pain comprising administering a pharmaceutical formulation according to claim 3 to a patient in need thereof.

5. A method of purifying a starting material of either oxymorphone or oxymorphone hydrochloride to yield the oxymorphone hydrochloride according to claim 1, comprising exposing the starting material oxymorphone or oxymorphone hydrochloride to hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C. for a time sufficient to provide the less than 10 ppm of 14-hydroxymorphinone.

6. The method according to claim 5, wherein the exposing is carried out for a period of at least 20 hours.

7. The method according to claim 5, wherein the reaction medium has a pH of less than 1.

8. The method according to claim 5, wherein the acid is hydrochloric acid.

9. The method according to claim 5, wherein the temperature is approximately 65° C.

10. The method according to claim 5, wherein the starting material oxymorphone or oxymorphone hydrochloride has not been isolated from a reaction mixture in which it is formed.

11. The method according to claim 5, wherein the starting material oxymorphone or oxymorphone hydrochloride has been prepared by a process comprising reduction of 14-hydroxymorphinone.

12. The method according to claim 11, wherein the 14-hydroxymorphinone that is reduced is prepared by a process of hydroxylating oripavine.

13. The method according to claim 12, wherein the oripavine is derived from concentrated poppy straw.

14. The method according to claim 13, wherein the concentrated poppy straw is derived from a high-Thebaine-yielding strain of poppy.

15. The method according to claim 5, comprising the additional steps of subsequently forming crystalline oxymorphone hydrochloride and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the crystalline oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

16. The method according to claim 15, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by exposure to reduced pressure.

17. The method according to claim 15, comprising the additional step of removing some of the water molecules from within the crystal structure of the oxymorphone hydrochloride by heating the oxymorphone hydrochloride to a temperature in the range of from 50 to 55° C. under reduced pressure.

18. A method of making hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and a KF of 6-8 wt %, comprising exposing a starting material of oxymorphone or oxymorphone hydrochloride to gaseous hydrogen under reducing conditions in a strongly acid water and alcohol solvent reaction medium at a temperature in the range from 60 to 70° C., subsequently forming crystalline oxymorphone hydrochloride, and removing residual alcohol molecules from within the crystal structure of the crystalline oxymorphone hydrochloride by exposing the oxymorphone hydrochloride to water vapour, such that the residual alcohol molecules are displaced with water molecules.

19. Hydrated oxymorphone hydrochloride having less than 10 ppm, as measured by HPLC, of 14-hydroxymorphinone and having peaks within the following 20 ranges when analyzed by Powder X-Ray Diffraction: 8.5-9.5, 11.0-12.0, 11.5-12.5, 12.4-13.4, 15.2-16.2, 17.6-18.6, 19.3-20.3, 19.9-20.9, 24.6-25.6, 24.9-25.9, 29.0-30.0 and 31.0-32.0.

20. Oxymorphone hydrochloride prepared by the method of claim 5.

21. Hydrated oxymorphone hydrochloride prepared by the method of claim 18.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

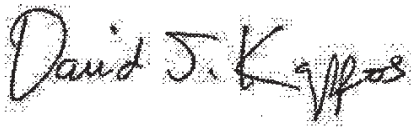
CERTIFICATE OF CORRECTION

PATENT NO.	: 7,851,482 B2
APPLICATION NO.	: 11/866840
DATED	: December 14, 2010
INVENTOR(S)	: Jen-Sen Dung et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 23, line 3, delete "20 ranges" and insert therefor --2Θ ranges--.

Signed and Sealed this
Nineteenth Day of July, 2011



David J. Kappos
Director of the United States Patent and Trademark Office

Exhibit B

(12) **United States Patent**
Kao et al.

(10) **Patent No.: US 8,309,122 B2**
(45) **Date of Patent: *Nov. 13, 2012**

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1344 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/680,432**

(22) Filed: **Feb. 28, 2007**

(65) **Prior Publication Data**

US 2007/0134328 A1 Jun. 14, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on Jul. 3, 2002.

(60) Provisional application No. 60/303,357, filed on Jul. 6, 2001, provisional application No. 60/329,432, filed on Oct. 15, 2001, provisional application No. 60/329,444, filed on Oct. 15, 2001, provisional application No. 60/329,445, filed on Oct. 15, 2001.

(51) **Int. Cl.**

A61K 9/22	(2006.01)
A61K 9/34	(2006.01)
A61K 9/36	(2006.01)

(52) **U.S. Cl.** **424/464**; 424/468; 424/470; 424/479; 424/481; 424/482; 424/486

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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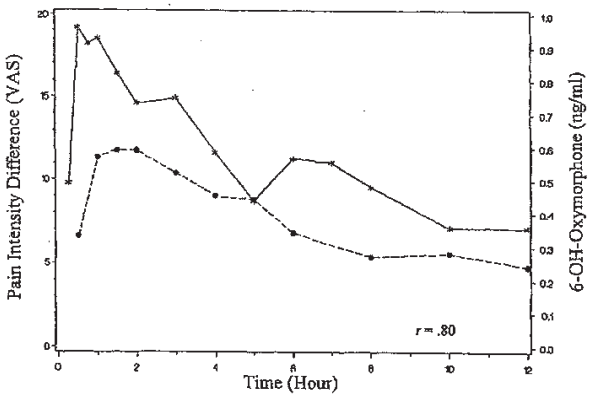
(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

20 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



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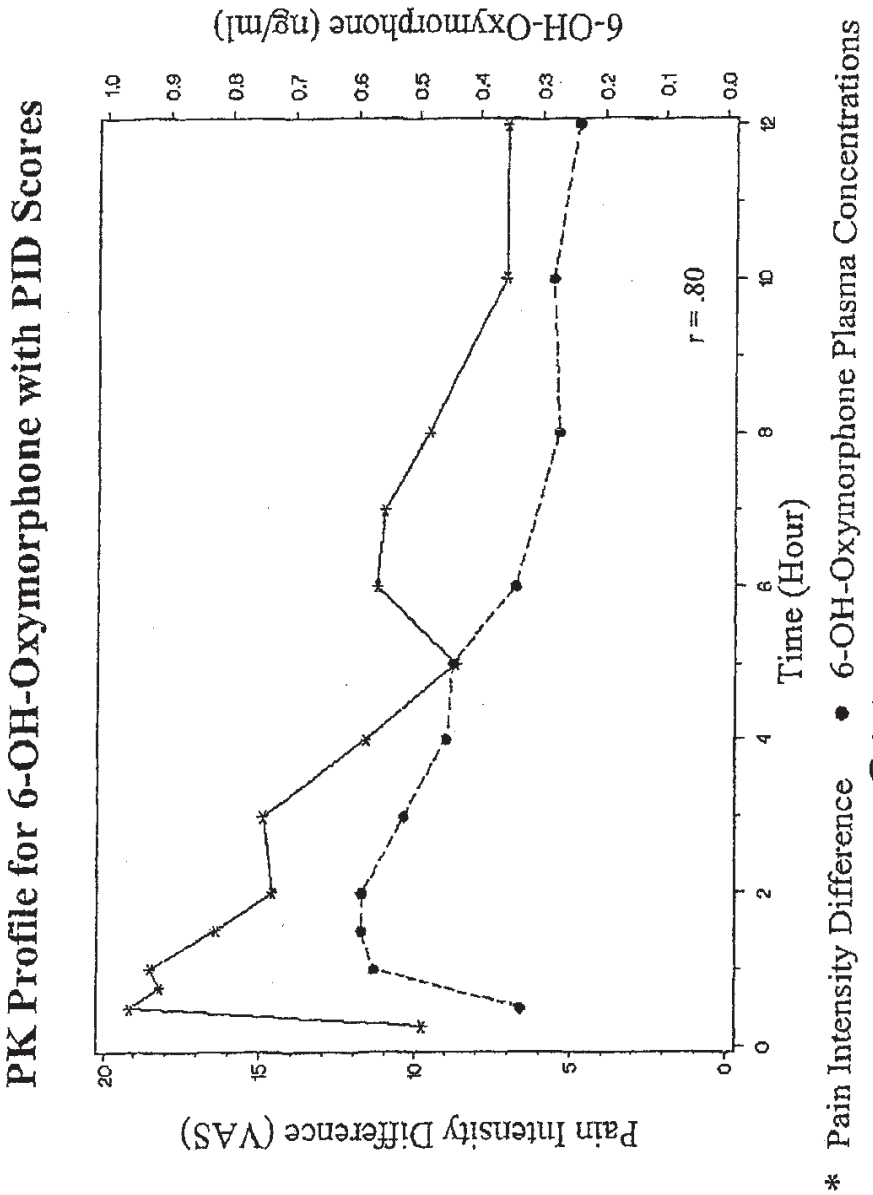
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6-OH-Oxymorphone (ng/ml)
Pain Intensity Difference (VAS)
Time (Hour)
r = .80
* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

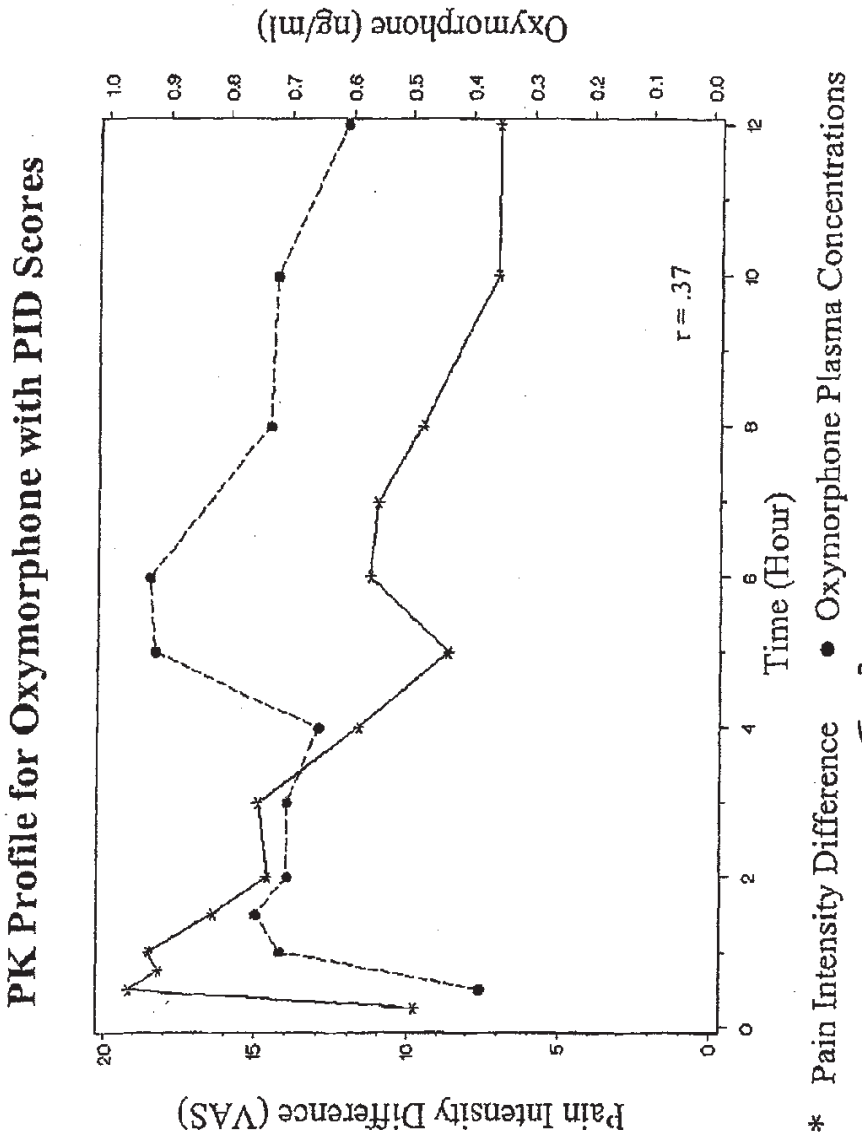
PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference • Oxymorphone Plasma Concentrations

FIG. 2

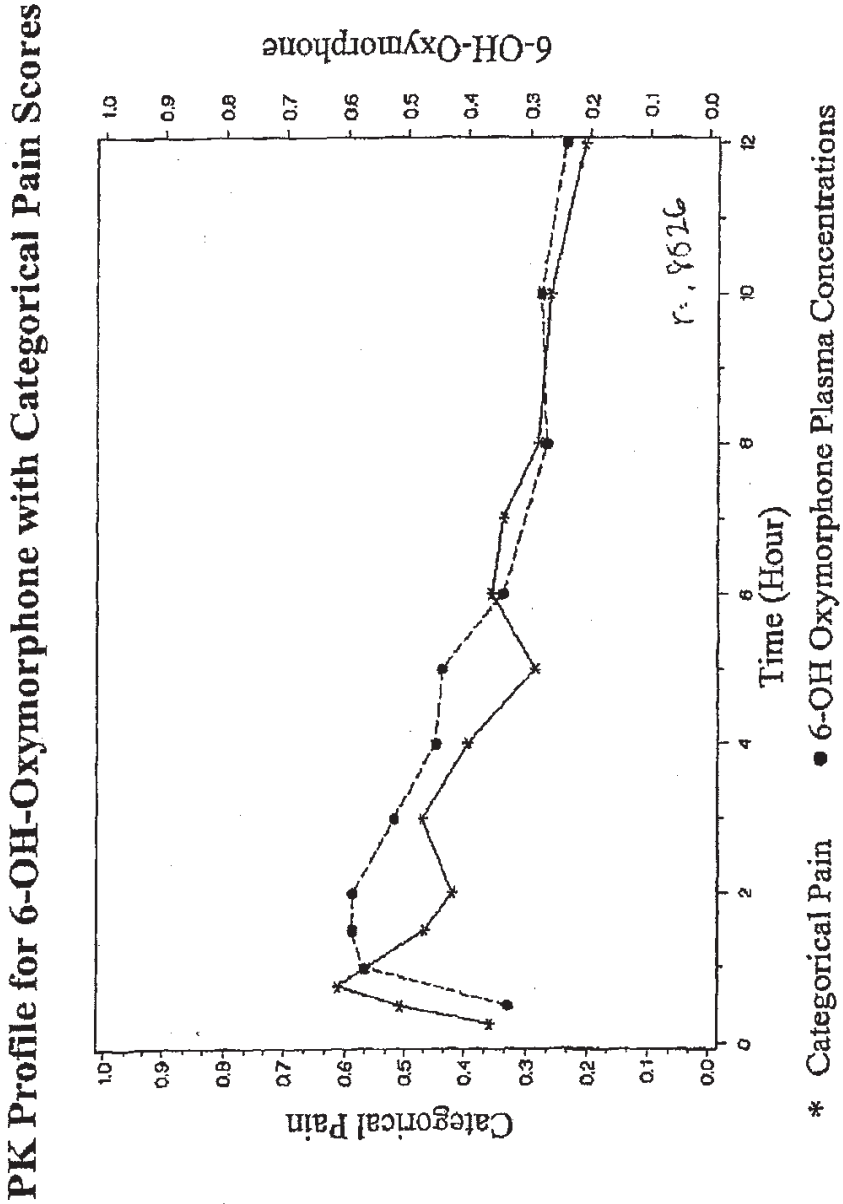
PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores
6-OH-Oxymorphone
Categorical Pain
Time (Hour)
r-, 9626
* Categorical Pain
● 6-OH Oxymorphone Plasma Concentrations

Fig. 3

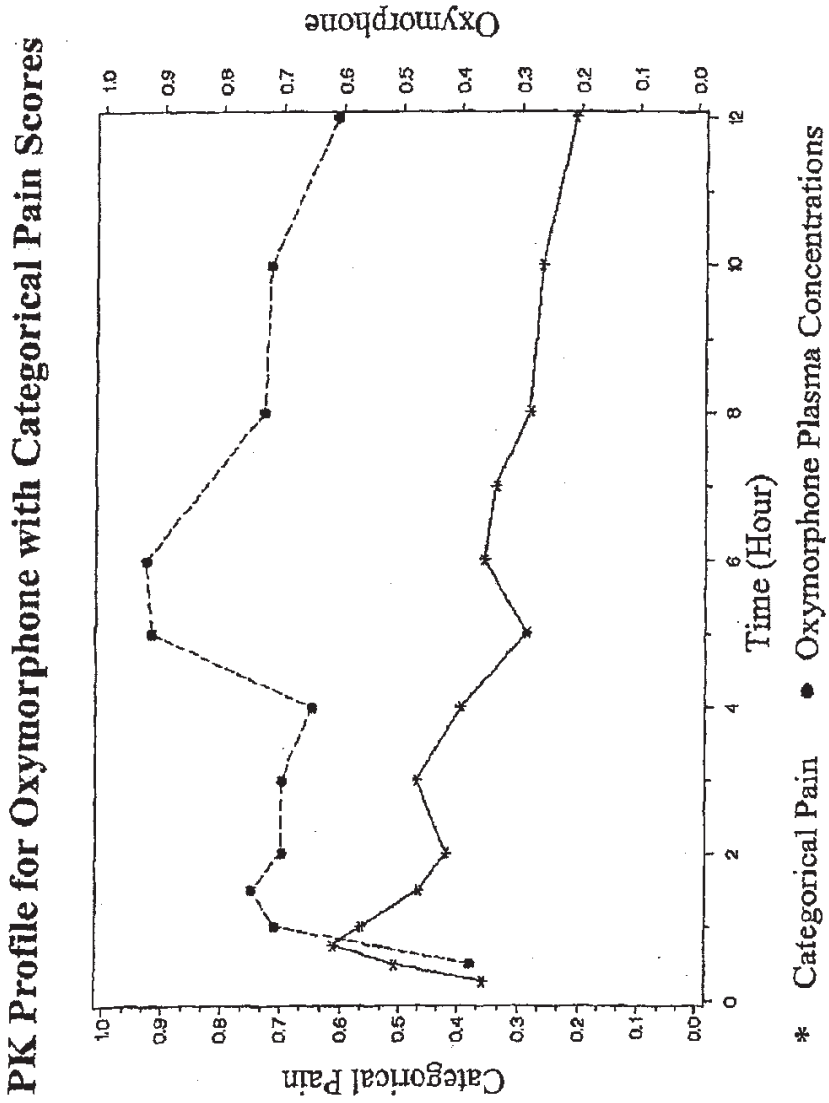
PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
● Oxymorphone Plasma Concentrations

FIG. 4

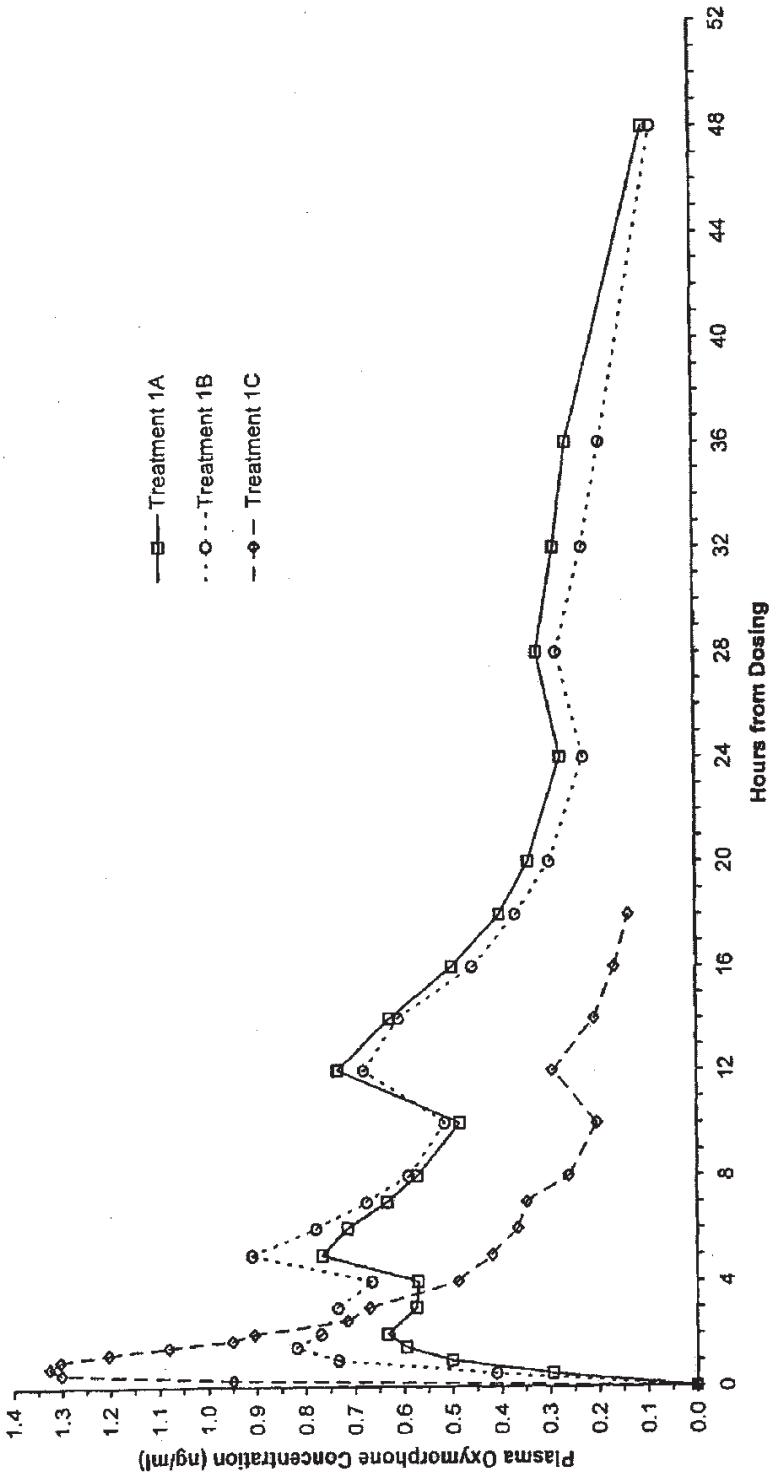
Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

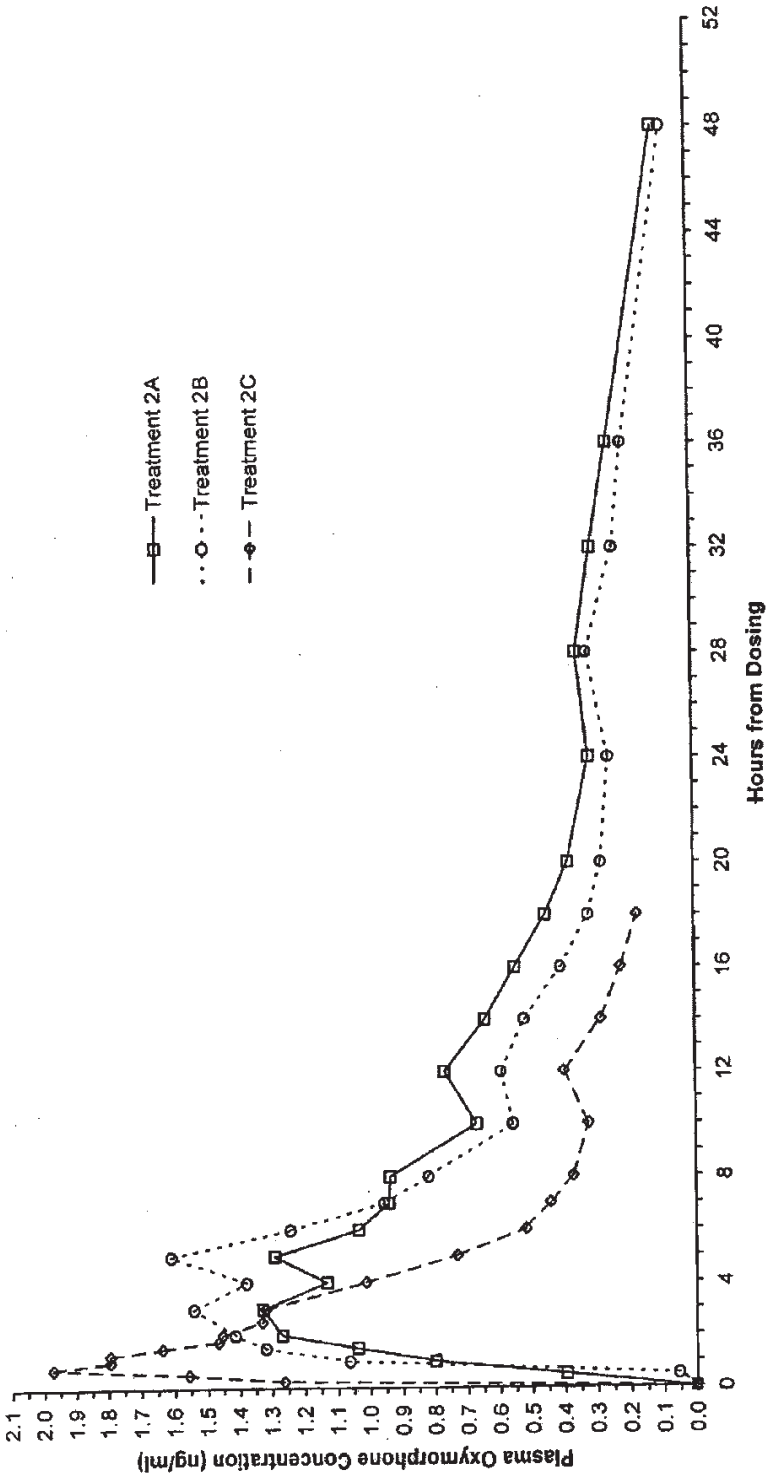
Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6

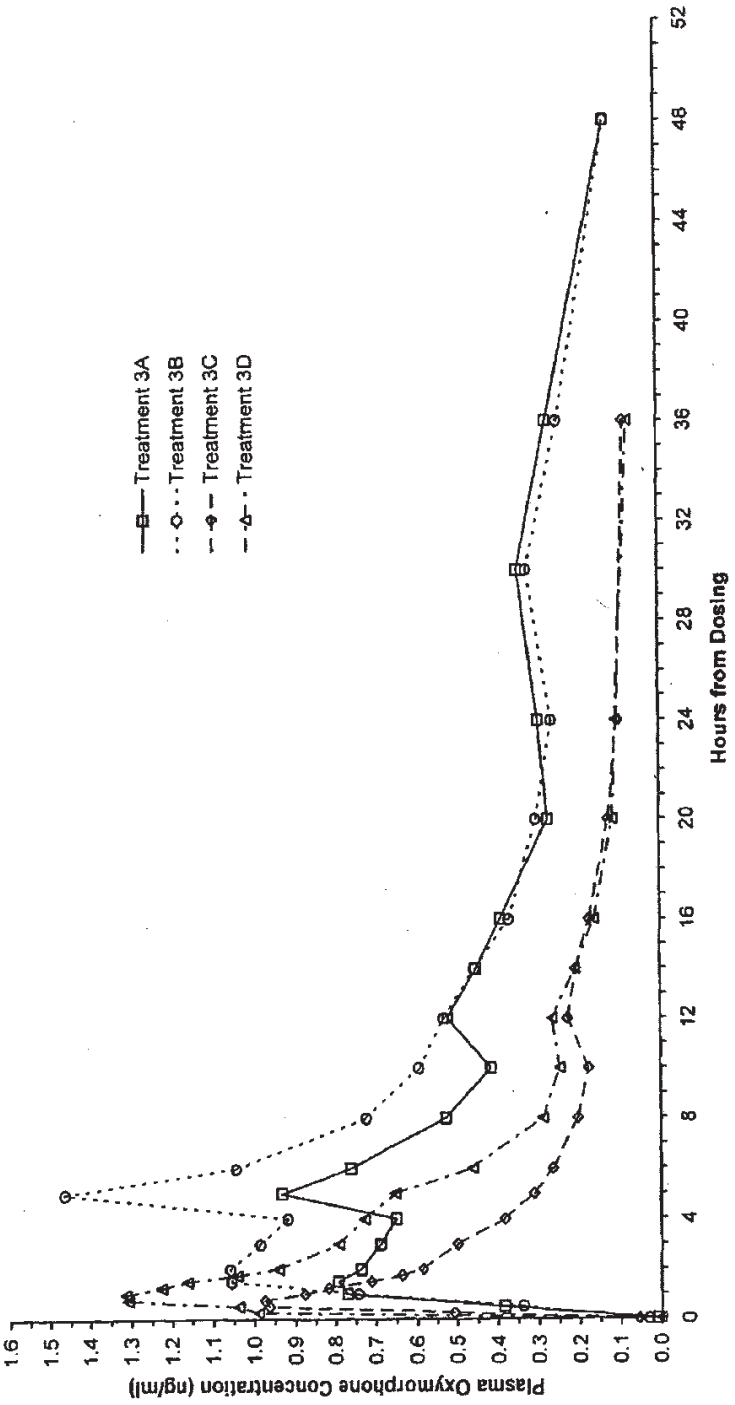
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 7

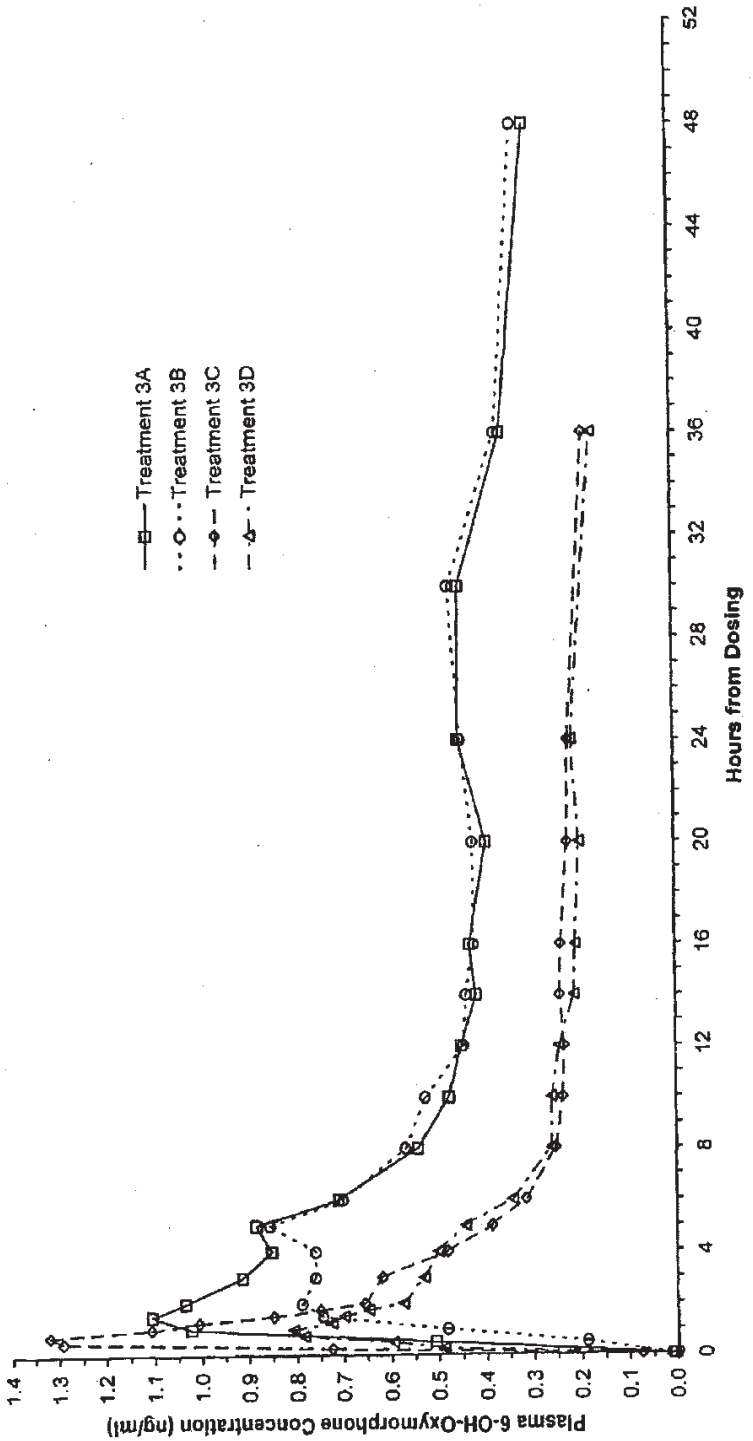
Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma 6-OH-Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 8

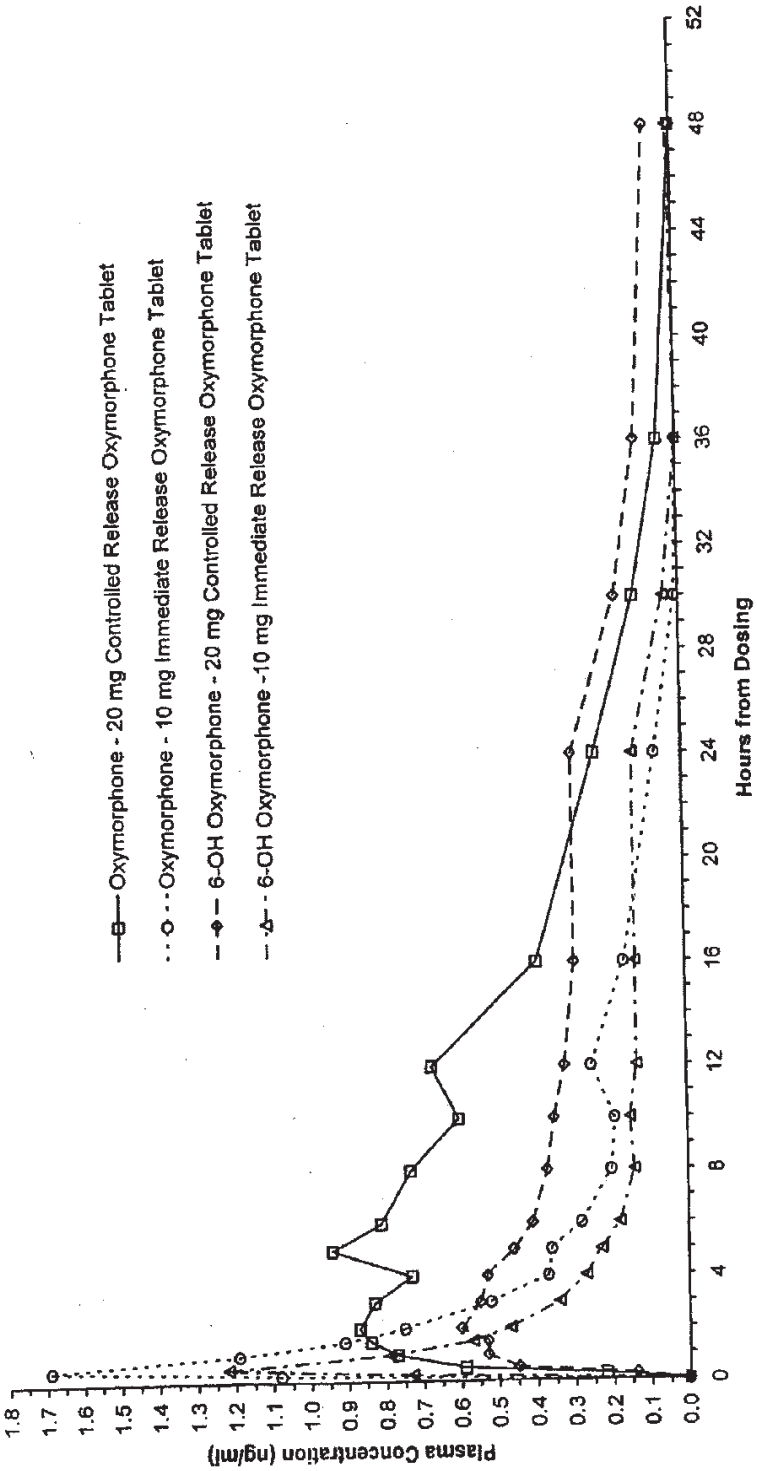
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

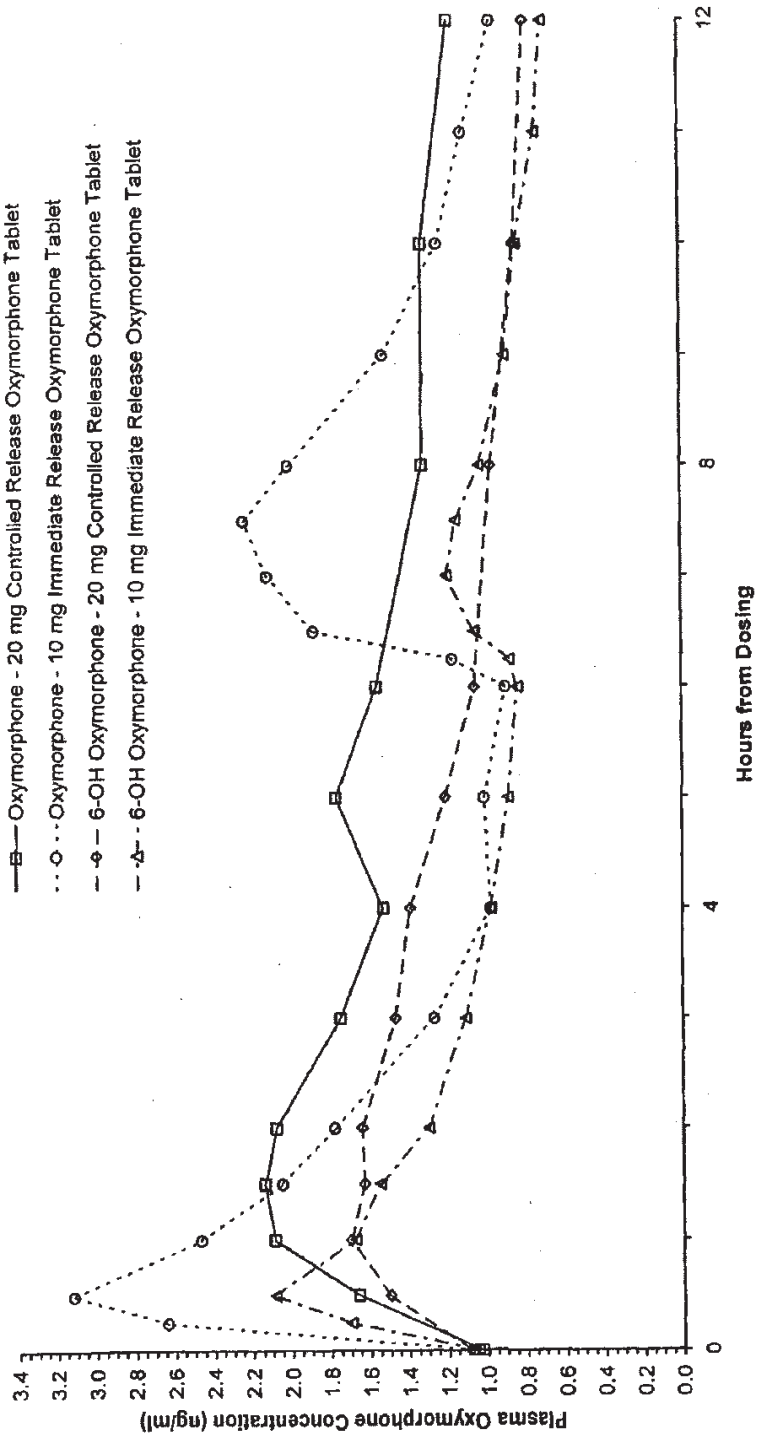
Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
0
4
8
12
Hours from Dosing

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. **1-2** show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10^6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according, to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$	Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.
$AUC_{(0-inf)}$	Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)} = AUC_{(0-t)} + Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.
$AUC_{(0-24)}$	Partial area under the drug concentration-time curve from time zero to 24 hours.
C_{max}	Maximum observed drug concentration.
T_{max}	Time of the observed maximum drug concentration.
K_{el}	Elimination rate constant based on the linear regression of the terminal linear portion of the LN(concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1—Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 ± 0.203	1.121 ± 0.211	1.108 ± 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-t)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 ± 0.098	0.783 ± 0.117	0.944 ± 0.110

Study 2—Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 ± 0.187	0.949 ± 0.154	1.148 ± 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}18)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 ± 0.105	0.694 ± 0.124	1.012 ± 0.175

As may be seen from tables 5 and 10 and FIGS. **1** and **2**, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T max much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3—One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. **7**. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.56	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
1.040 ± 0.1874	0.8863 ± 0.2569	1.368 ± 0.4328	1.169 ± 0.2041

TABLE 16

Relative Bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3B vs. 3A)
0.9598 ± 0.2151	0.8344 ± 0.100	1.470 ± 0.3922	1.299 ± 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max}(approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxyoxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max} was later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under the fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxyoxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ration for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-values duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxyoxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normal-

ized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicted similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment.

Bioavailability of 6-hydroxyoxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max}, was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877

TABLE 17-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma 6-Hydroxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(o-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(o-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4—Controlled Release 20 mg vs. Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. 9 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed

by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. 9 in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. 10 shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. 10 in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88

TABLE 20-continued

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
$AUC_{(o-t)}$	14.74	11.54	7.10	5.66
$AUC_{(o-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½ (hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(o-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(o-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma, concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified, using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5—Controlled Release 40 mg vs. Immediate Release 4.times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times. 10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(o-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(o-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(t-72)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma 6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(o-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(o-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet, and a controlled release delivery system comprising at least one pharmaceutical excipient, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

2. The pharmaceutical composition of claim 1 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test.

3. The pharmaceutical composition of claim 1 wherein at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

4. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid.

5. The pharmaceutical composition of claim 1 wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

6. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

7. The pharmaceutical composition of claim 5 wherein the heteropolysaccharide comprises xanthan gum or deacylated xanthan gum.

8. The pharmaceutical composition of claim 5 wherein the agent capable of cross-linking the heteropolysaccharide comprises a homopolysaccharide gum.

9. The pharmaceutical composition of claim 8 wherein the homopolysaccharide gum comprises locust bean gum.

10. The pharmaceutical composition of claim 1 wherein the controlled release delivery system further comprises a hydrophobic polymer.

11. The pharmaceutical composition of claim 10 wherein the hydrophobic polymer comprises an alkylcellulose.

12. The pharmaceutical composition of claim 8 further comprising a cationic cross-linking agent.

13. The pharmaceutical composition of claim 12 wherein the cationic cross-linking agent is selected from calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate, sodium fluoride, and combinations thereof.

14. The pharmaceutical composition of claim 13 wherein the cationic cross-linking agent is present in an amount of about 0.5% to about 16%, by weight of the composition.

15. The pharmaceutical composition of claim 5 wherein the weight ratio of heteropolysaccharide to oxymorphone or pharmaceutically acceptable salt thereof is about 10:1 to about 1:10.

16. The pharmaceutical composition of claim 1 wherein oxymorphone or pharmaceutically acceptable salt thereof is present in an amount of about 5 mg to about 80 mg.

17. The pharmaceutical composition of claim 5 wherein the controlled release delivery system comprises about 10% to about 99% of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, about 1% to about 20% of a cationic crosslinking agent, and about 0% to about 89% of other ingredients which qualify as an inert pharmaceutical diluent, by total weight of the controlled release delivery system.

18. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim 1 comprising about 5 mg to about 80 mg of oxymorphone or pharmaceutically acceptable salt thereof.

19. An analgesically effective controlled release pharmaceutical composition with a twelve hour dosing interval in the form of a tablet, comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient in the tablet and a controlled release delivery system comprising a hydrophilic material that forms a gel upon exposure to gastrointestinal fluid, wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8

at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the composition at about 10 hours in the test.

20. The method of claim **18** wherein upon oral administration of the composition the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the composition is administered to the subject under fed as compared to fasted conditions.

* * * * *

Exhibit C

US008329216B2

(12) **United States Patent**
Kao et al.

(10) **Patent No.: US 8,329,216 B2**
(45) **Date of Patent: *Dec. 11, 2012**

(54) **OXYMORPHONE CONTROLLED RELEASE FORMULATIONS**

(75) Inventors: **Haui-Hung Kao**, Syosset, NY (US); **Anand R. Baichwal**, Wappingers Falls, NY (US); **Troy McCall**, Smyrna, GA (US); **David Lee**, Chadds, PA (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1192 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/427,438**

(22) Filed: **Jun. 29, 2006**

(65) **Prior Publication Data**

US 2007/0098794 A1 May 3, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/190,192, filed on Jul. 3, 2002.

(60) Provisional application No. 60/329,445, filed on Oct. 15, 2001, provisional application No. 60/329,432, filed on Oct. 15, 2001, provisional application No. 60/303,357, filed on Jul. 6, 2001, provisional application No. 60/329,444, filed on Oct. 15, 2001.

(51) **Int. Cl.**

A61K 9/22	(2006.01)
A61K 9/34	(2006.01)
A61K 9/36	(2006.01)

(52) **U.S. Cl.** **424/464**; 424/468; 424/470; 424/479; 424/481; 424/482; 424/486

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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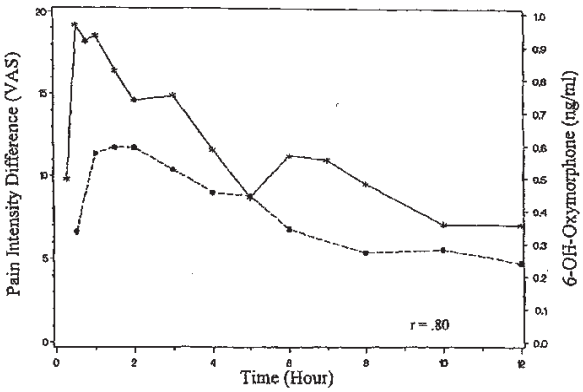
(57) **ABSTRACT**

The invention pertains to a method of relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces a mean minimum blood plasma level 12 to 24 hours after dosing, as well as the tablet producing the sustained pain relief.

82 Claims, 10 Drawing Sheets

PK Profile for 6-OH-Oxymorphone with PID Scores



* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

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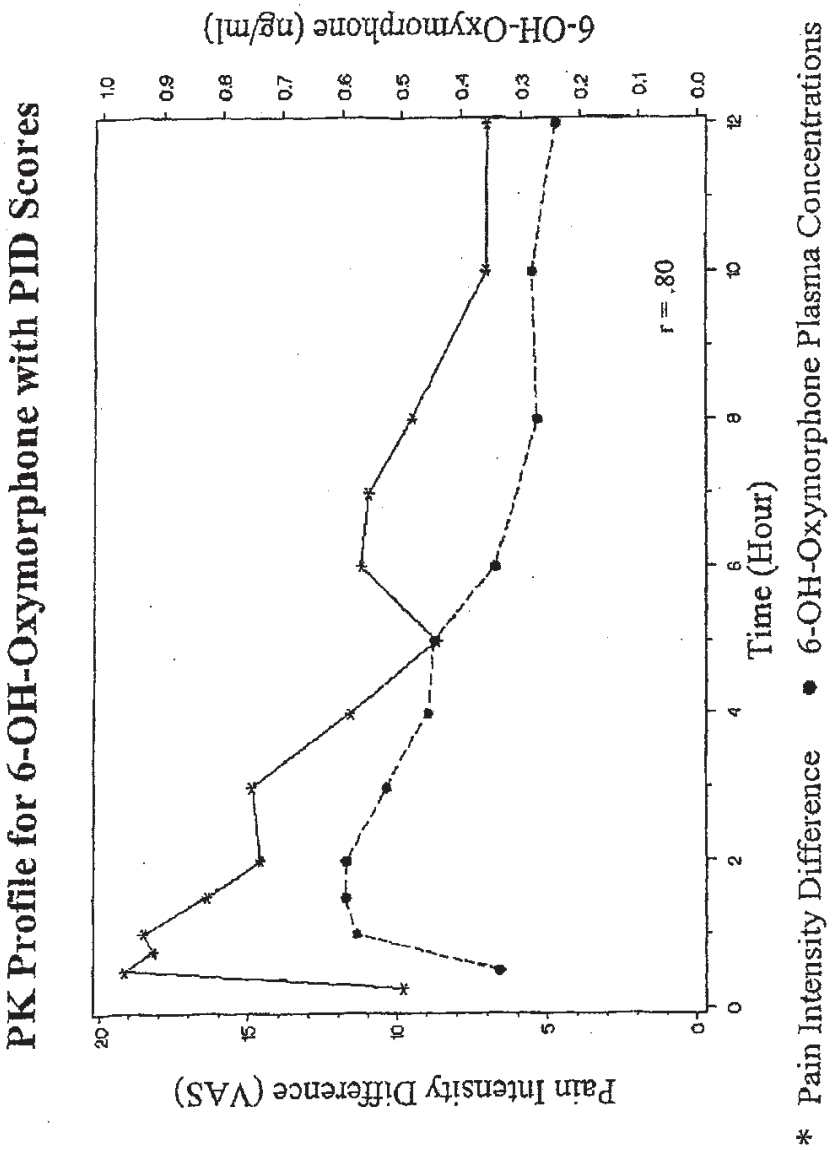

PK Profile for 6-OH-Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
6-OH-Oxymorphone (ng/ml)
Time (Hour)
r = .80
* Pain Intensity Difference • 6-OH-Oxymorphone Plasma Concentrations

FIG. 1

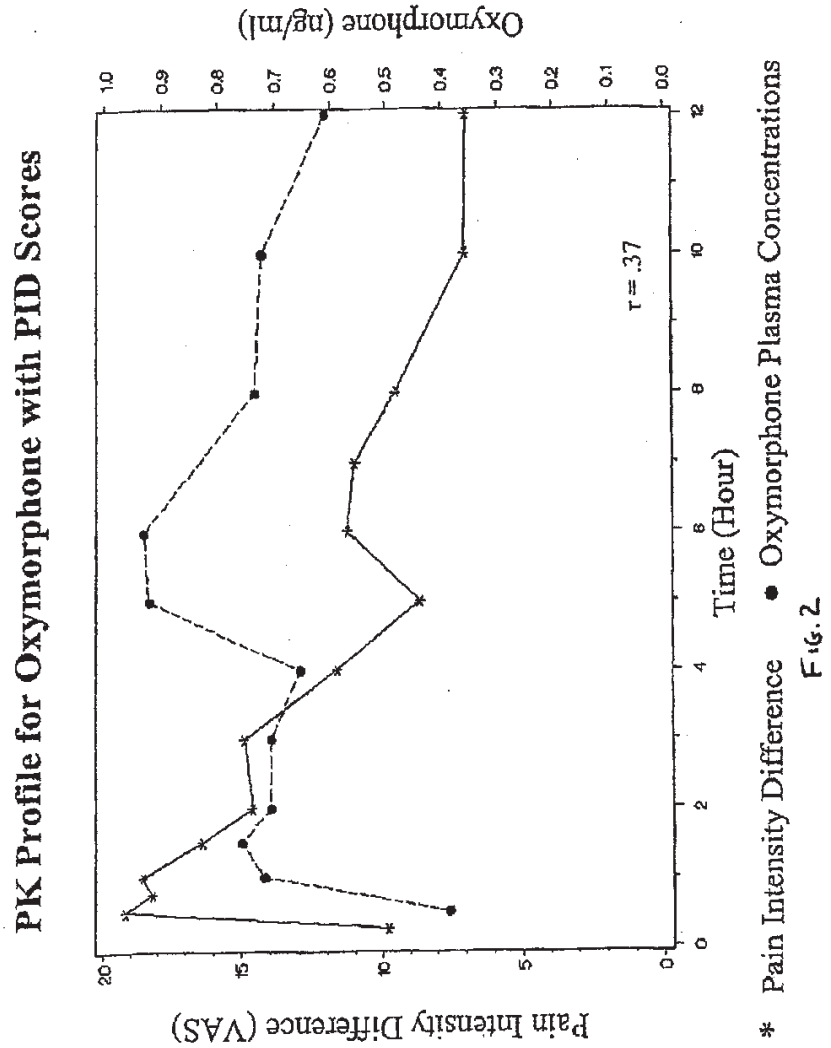
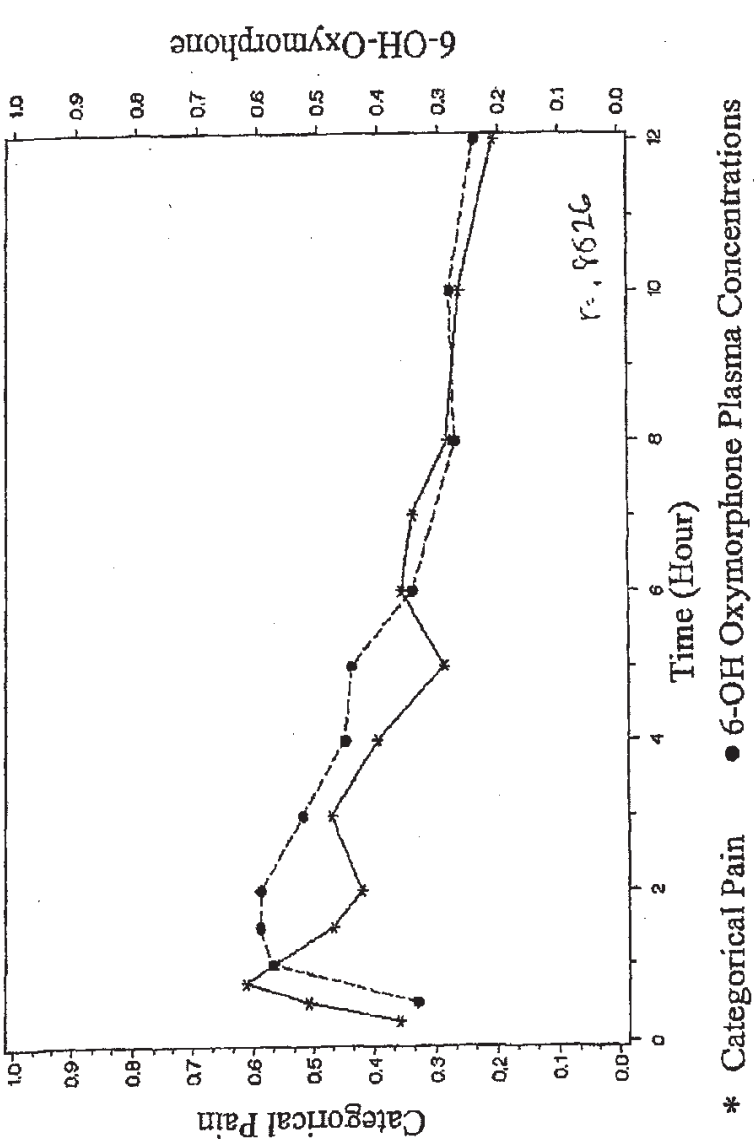

PK Profile for Oxymorphone with PID Scores
Pain Intensity Difference (VAS)
Oxymorphone (ng/ml)
Time (Hour)
r = .37
* Pain Intensity Difference • Oxymorphone Plasma Concentrations

Fig. 2

PK Profile for 6-OH-Oxymorphone with Categorical Pain Scores



* Categorical Pain ● 6-OH Oxymorphone Plasma Concentrations

FIG. 3

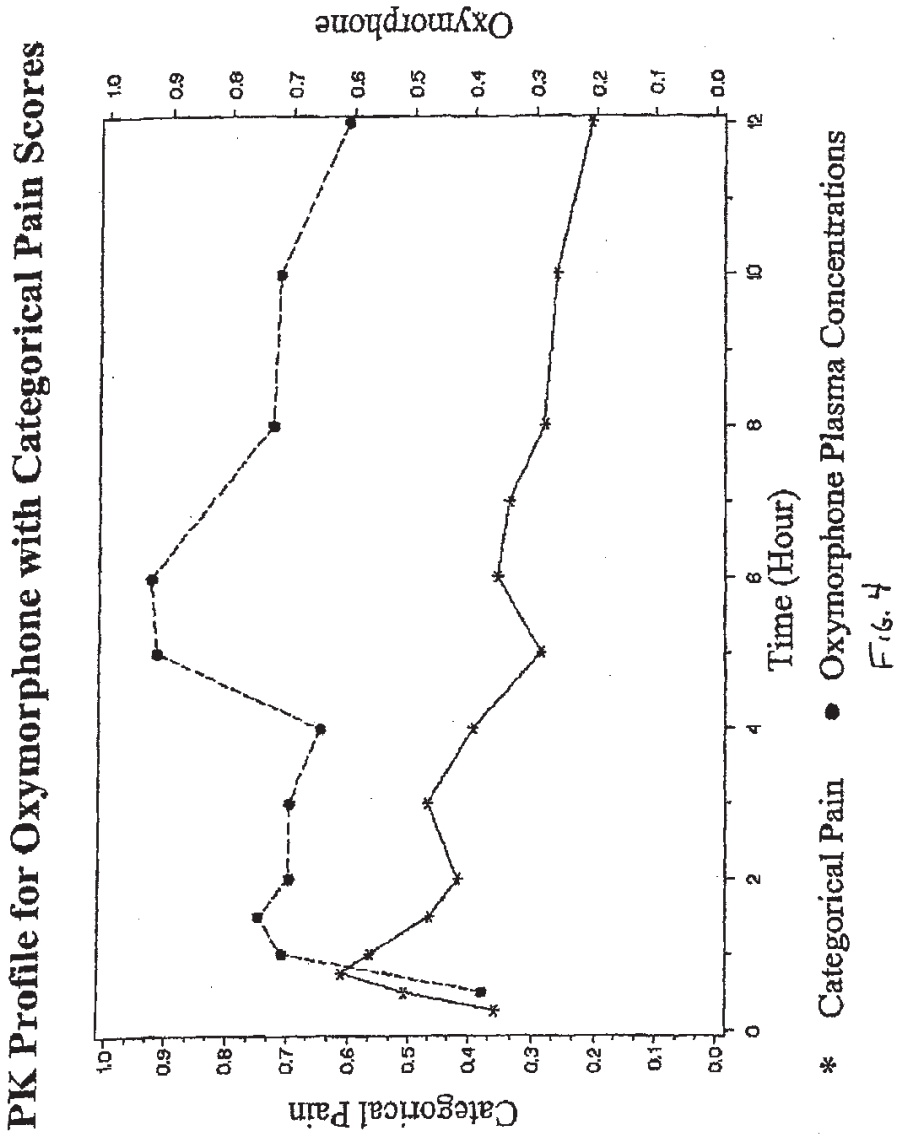

PK Profile for Oxymorphone with Categorical Pain Scores
Oxymorphone
Categorical Pain
Time (Hour)
* Categorical Pain
● Oxymorphone Plasma Concentrations

FIG. 4

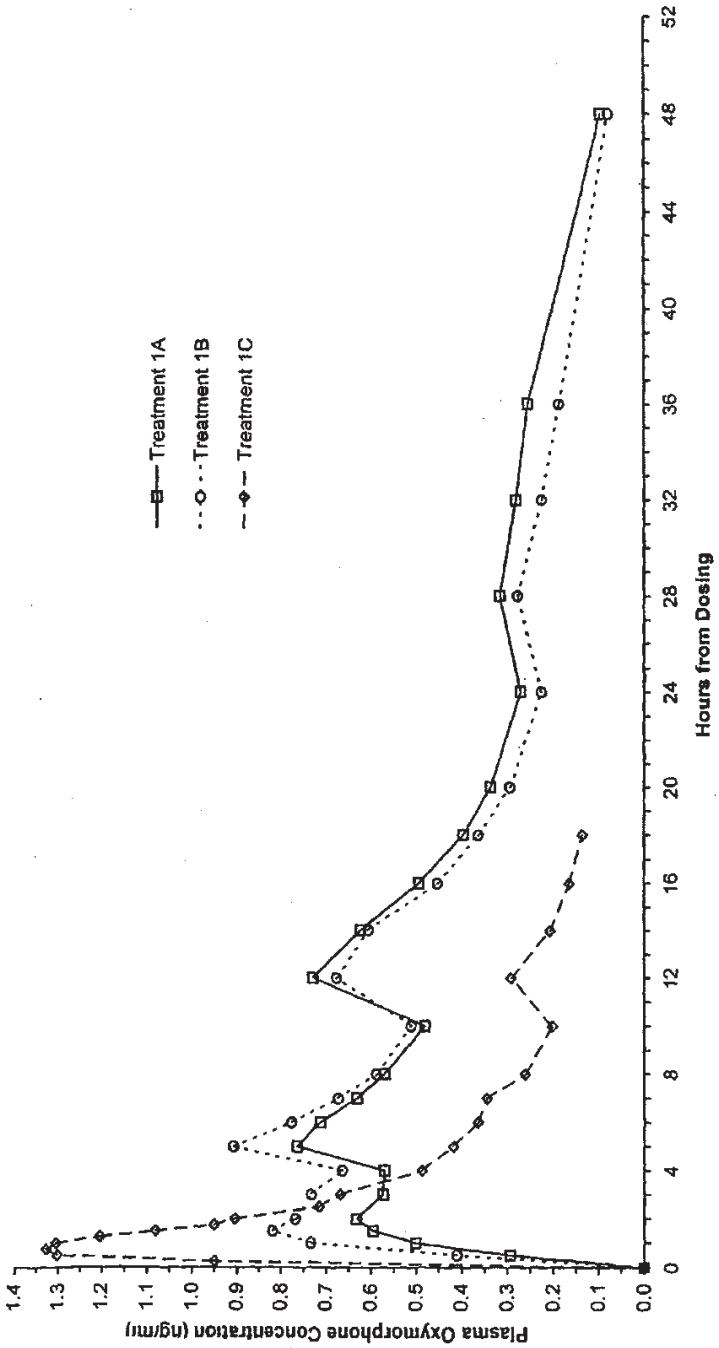

Treatment 1A
Treatment 1B
Treatment 1C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 5

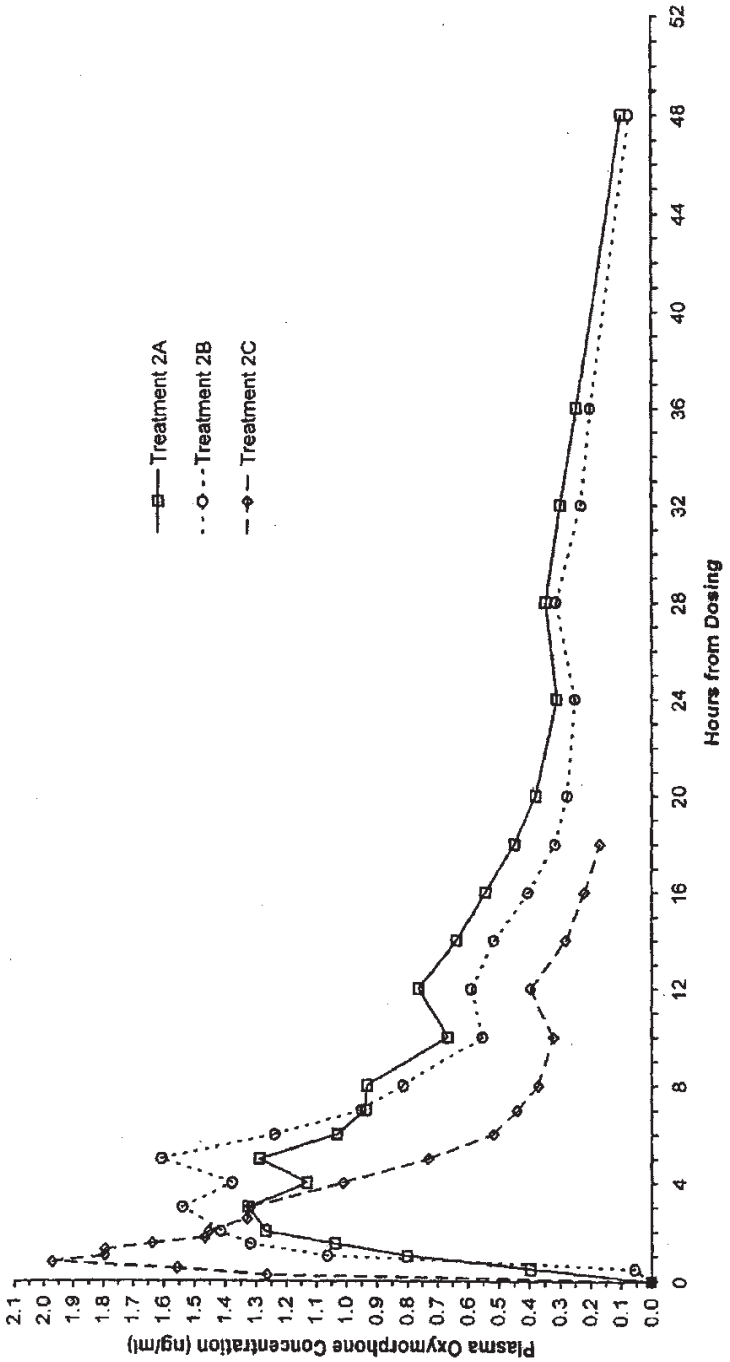
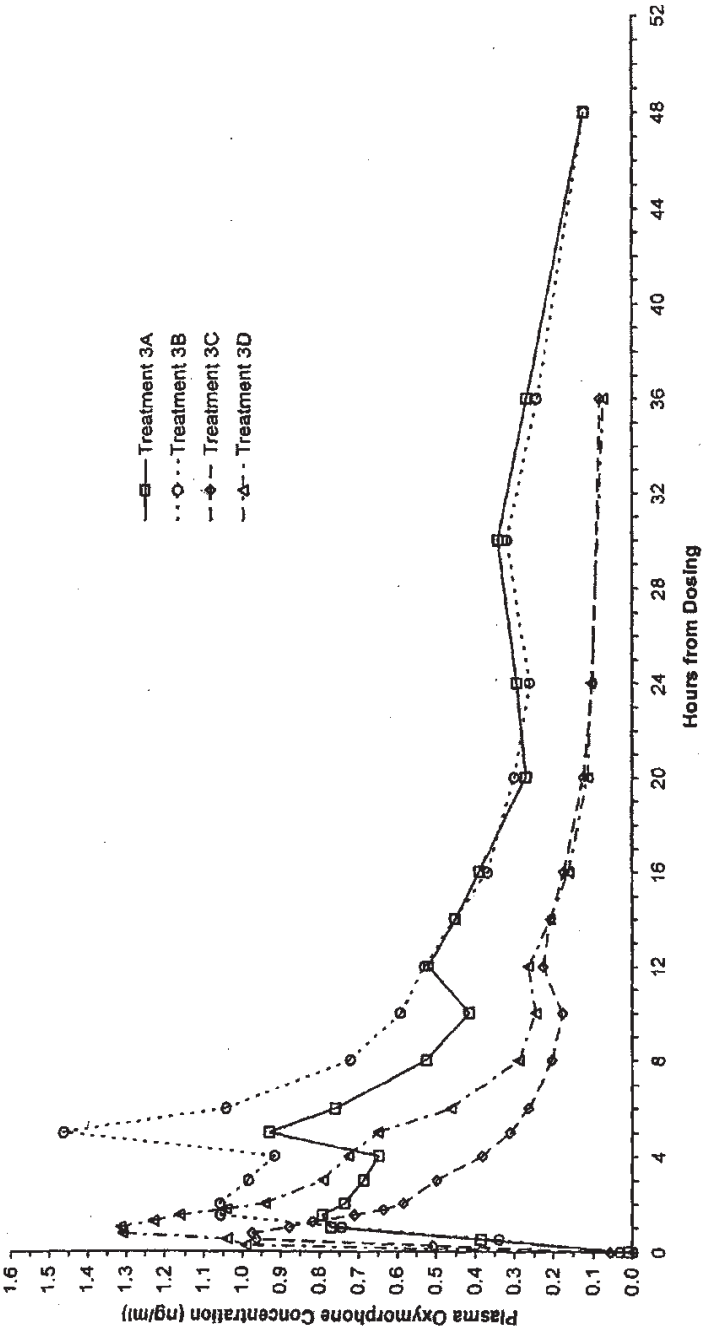

Treatment 2A
Treatment 2B
Treatment 2C
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 6


Treatment 3A
Treatment 3B
Treatment 3C
Treatment 3D
Plasma Oxymorphone Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
0
4
8
12
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36
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44
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52

Figure 7

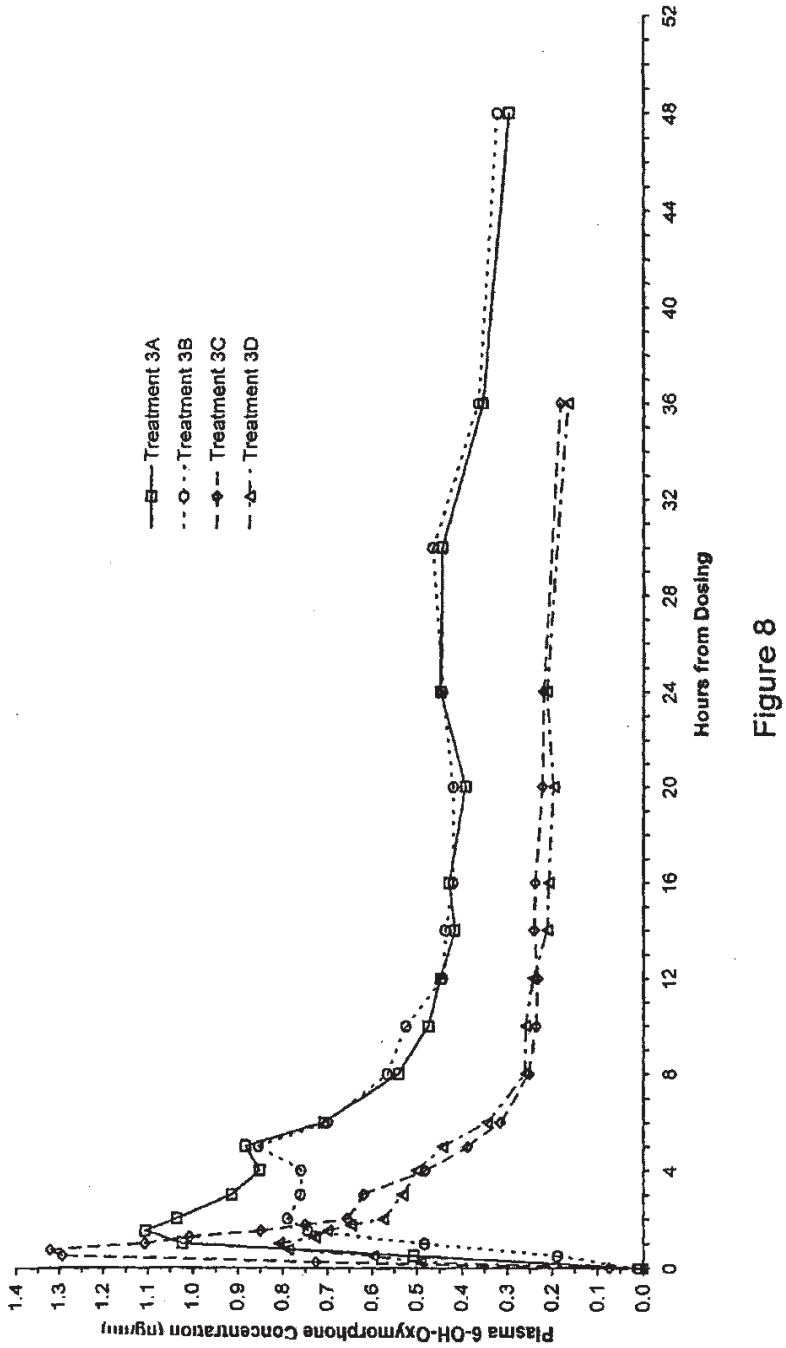


Figure 8

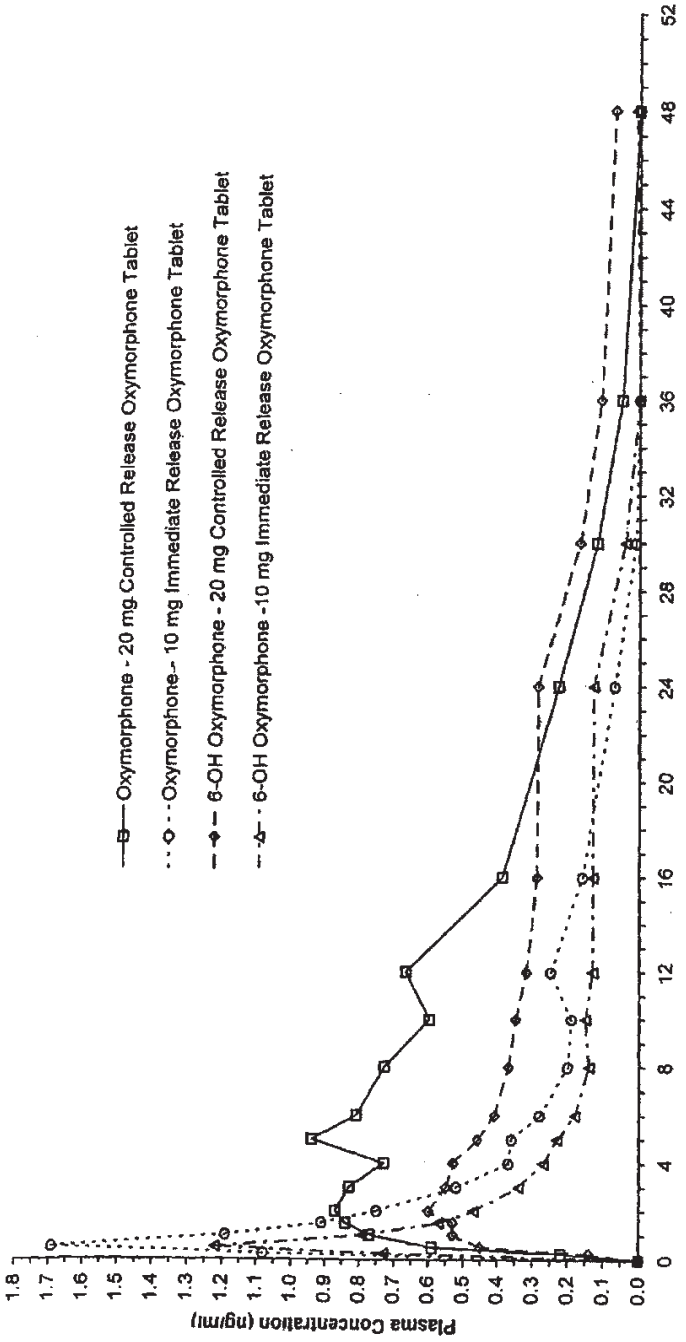

Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone- 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone -10 mg Immediate Release Oxymorphone Tablet
Plasma Concentration (ng/ml)
Hours from Dosing
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
0
4
8
12
16
20
24
28
32
36
40
44
48
52

Figure 9

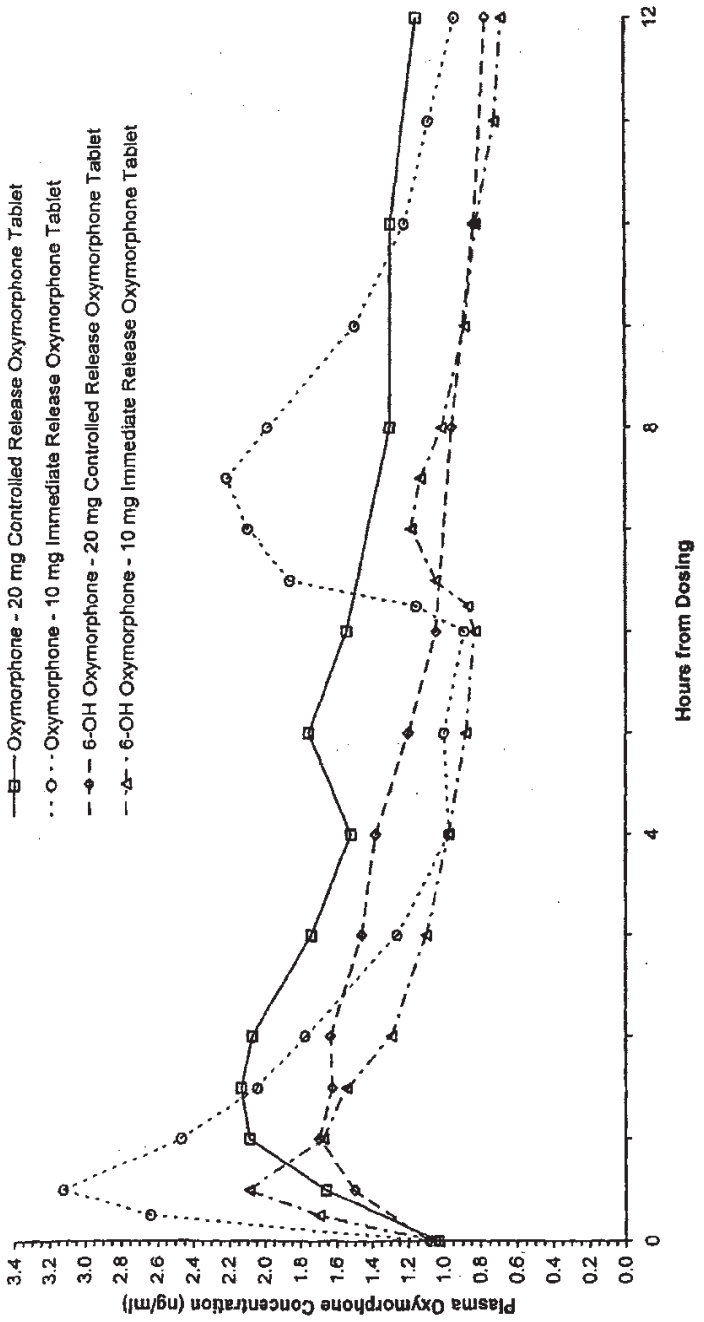

Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
6-OH Oxymorphone - 20 mg Controlled Release Oxymorphone Tablet
6-OH Oxymorphone - 10 mg Immediate Release Oxymorphone Tablet
Plasma Oxymorphone Concentration (ng/ml)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
0
4
8
12
Hours from Dosing

Figure 10

OXYMORPHONE CONTROLLED RELEASE FORMULATIONS

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/190,192 filed Jul. 3, 2002 and claims priority to U.S. Provisional Patent Application Ser. Nos. 60/329,445 filed Oct. 15, 2001, 60/329,432 filed Oct. 15, 2001, 60/303,357 filed Jul. 6, 2001, and 60/329,444 filed Oct. 15, 2001, which are incorporated herein by reference to the extent permitted by law.

BACKGROUND OF THE INVENTION

Pain is the most frequently reported symptom and it is a common clinical problem which confronts the clinician. Many millions of people in the USA suffer from severe pain that, according to numerous recent reports, is chronically undertreated or inappropriately managed. The clinical usefulness of the analgesic properties of opioids has been recognized for centuries, and morphine and its derivatives have been widely employed for analgesia for decades in a variety of clinical pain states.

Oxymorphone HCl (14-hydroxydihydromorphinone hydrochloride) is a semi-synthetic phenanthrene-derivative opioid agonist, widely used in the treatment of acute and chronic pain, with analgesic efficacy comparable to other opioid analgesics. Oxymorphone is currently marketed as an injection (1 mg/ml in 1 ml ampules; 1.5 mg/ml in 1 ml ampules; 1.5 mg/ml in 10 ml multiple dose vials) for intramuscular, subcutaneous, and intravenous administration, and as 5 mg rectal suppositories. At one time, 2 mg, 5 mg and 10 mg oral immediate release (IR) tablet formulations of oxymorphone HCl were marketed. Oxymorphone HCl is metabolized principally in the liver and undergoes conjugation with glucuronic acid and reduction to 6-alpha- and beta-hydroxy epimers.

An important goal of analgesic therapy is to achieve continuous relief of chronic pain. Regular administration of an analgesic is generally required to ensure that the next dose is given before the effects of the previous dose have worn off. Compliance with opioids increases as the required dosing frequency decreases. Non-compliance results in suboptimal pain control and poor quality of life outcomes. (Ferrell B et al. Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26). Scheduled, rather than "as needed" administration of opioids is currently recommended in guidelines for their use in chronic non-malignant pain. Unfortunately, evidence from prior clinical trials and clinical experience suggests that the short duration of action of immediate release oxymorphone would necessitate administration every 4-6 hours in order to maintain optimal levels of analgesia in chronic pain. A controlled release formulation which would allow less frequent dosing of oxymorphone would be useful in pain management.

For instance, a controlled release formulation of morphine has been demonstrated to provide patients fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of pain. In addition, the controlled release formulation of morphine was reported to provide more constant plasma concentration and clinical effects, less frequent peak to trough fluctuations, reduced dosing frequency, and possibly fewer side effects. (Thirlwell M P et al., Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. *Cancer* 1989; 63:2275-83; Goughnour B R et al., Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. *Cancer* 1989; 63:2294-97; Ferrell B. et al., Effects of controlled-release morphine on quality of life for cancer pain. *Oncol. Nur. Forum* 1989; 4:521-26.

There are two factors associated with the metabolism of some drugs that may present problems for their use in controlled release systems. One is the ability of the drug to induce or inhibit enzyme synthesis, which may result in a fluctuating drug blood plasma level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Oxymorphone is metabolized principally in the liver, resulting in an oral bioavailability of about 10%. Evidence from clinical experience suggests that the short duration of action of immediate release oxymorphone necessitates a four hour dosing schedule to maintain optimal levels of analgesia. It would be useful to clinicians and patients alike to have controlled release dosage forms of oxymorphone to use to treat pain and a method of treating pain using the dosage forms.

SUMMARY OF THE INVENTION

The present invention provides methods for relieving pain by administering a controlled release pharmaceutical tablet containing oxymorphone which produces at least a predetermined minimum blood plasma level for at least 12 hours after dosing, as well as tablets that produce the sustained pain relief over this time period.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a pharmacokinetic profile for 6-hydroxy oxymorphone with PID scores.

FIG. **2** is a pharmacokinetic profile for oxymorphone with PID scores.

FIG. **3** is a pharmacokinetic profile for 6-hydroxy oxymorphone with categorical pain scores.

FIG. **4** is a pharmacokinetic profile for oxymorphone with categorical pain scores.

FIG. **5** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 1.

FIG. **6** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 2.

FIG. **7** is a graph of the mean blood plasma concentration of oxymorphone versus time for clinical study 3.

FIG. **8** is a graph of the mean blood plasma concentration of 6-hydroxy oxymorphone versus time for clinical study 3.

FIG. **9** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a single dose study.

FIG. **10** is a graph of the mean blood plasma concentration of oxymorphone for immediate and controlled release tablets from a steady state study.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods for alleviating pain for 12 to 24 hours using a single dose of a pharmaceutical composition by producing a blood plasma level of oxymorphone and/or 6-OH oxymorphone of at least a minimum value for at least 12 hours or more. As used herein, the terms "6-OH oxymorphone" and "6-hydroxy oxymorphone" are interchangeable and refer to the analog of oxymorphone hav-

ing an alcohol (hydroxy) moiety that replaces the carboxy moiety found on oxymorphone at the 6-position.

To overcome the difficulties associated with a 4-6 hourly dosing frequency of oxymorphone, this invention provides an oxymorphone controlled release oral solid dosage form, comprising a therapeutically effective amount of oxymorphone or a pharmaceutically acceptable salt of oxymorphone. It has been found that the decreased rate of release of oxymorphone from the oral controlled release formulation of this invention does not substantially decrease the bioavailability of the drug as compared to the same dose of a solution of oxymorphone administered orally. The bioavailability is sufficiently high and the release rate is such that a sufficient plasma level of oxymorphone and/or 6-OH oxymorphone is maintained to allow the controlled release dosage to be used to treat patients suffering moderate to severe pain with once or twice daily dosing. The dosing form of the present invention can also be used with thrice daily dosing.

It is critical when considering the present invention that the difference between a controlled release tablet and an immediate release formulation be fully understood. In classical terms, an immediate release formulation releases at least 80% of its active pharmaceutical ingredient within 30 minutes. With reference to the present invention, the definition of an immediate release formulation will be broadened further to include a formulation which releases more than about 80% of its active pharmaceutical ingredient within 60 minutes in a standard USP Paddle Method dissolution test at 50 rpm in 500 ml media having a pH of between 1.2 and 6.8 at 37° C. "Controlled release" formulations, as referred to herein, will then encompass any formulations which release no more than about 80% of their active pharmaceutical ingredients within 60 minutes under the same conditions.

The controlled release dosage form of this invention exhibits a dissolution rate in vitro, when measured by USP Paddle Method at 50 rpm in 500 ml media having a pH between 1.2 and 6.8 at 37° C., of about 15% to about 50% by weight oxymorphone released after 1 hour, about 45% to about 80% by weight oxymorphone released after 4 hours, and at least about 80% by weight oxymorphone released after 10 hours.

When administered orally to humans, an effective controlled release dosage form of oxymorphone should exhibit the following in vivo characteristics: (a) peak plasma level of oxymorphone occurs within about 1 to about 8 hours after administration; (b) peak plasma level of 6-OH oxymorphone occurs within about 1 to about 8 hours after administration; (c) duration of analgesic effect is through about 8 to about 24 hours after administration; (d) relative oxymorphone bioavailability is in the range of about 0.5 to about 1.5 compared to an orally-administered aqueous solution of oxymorphone; and (e) the ratio of the area under the curve of blood plasma level vs. time for 6-OH oxymorphone compared to oxymorphone is in the range of about 0.5 to about 1.5. Of course, there is variation of these parameters among subjects, depending on the size and weight of the individual subject, the subject's age, individual metabolism differences, and other factors. Indeed, the parameters may vary in an individual from day to day. Accordingly, the parameters set forth above are intended to be mean values from a sufficiently large study so as to minimize the effect of individual variation in arriving at the values. A convenient method for arriving at such values is by conducting a study in accordance with standard FDA procedures such as those employed in producing results for use in a new drug application (or abbreviated new drug application) before the FDA. Any reference to mean values herein, in conjunction with desired results, refer to results from such a study, or some comparable study. Reference to mean values reported herein for studies actually conducted are arrived at using standard statistical methods as would be employed by one skilled in the art of pharmaceutical formulation and testing for regulatory approval.

In one specific embodiment of the controlled release matrix form of the invention, the oxymorphone or salt of oxymorphone is dispersed in a controlled release delivery system that comprises a hydrophilic material which, upon exposure to gastrointestinal fluid, forms a gel matrix that releases oxymorphone at a controlled rate. The rate of release of oxymorphone from the matrix depends on the drug's partition coefficient between components of the matrix and the aqueous phase within the gastrointestinal tract. In a preferred form of this embodiment, the hydrophilic material of the controlled release delivery system comprises a mixture of a heteropolysaccharide gum and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid. The controlled release delivery system may also comprise a water-soluble pharmaceutical diluent mixed with the hydrophilic material. Preferably, the cross-linking agent is a homopolysaccharide gum and the inert pharmaceutical diluent is a monosaccharide, a disaccharide, or a polyhydric alcohol, or a mixture thereof.

In a specific preferred embodiment, the appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone are achieved using oxymorphone in the form of oxymorphone hydrochloride, wherein the weight ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:3 to about 3:1, the weight ratio of heteropolysaccharide to diluent is in the range of about 1:8 to about 8:1, and the weight ratio of heteropolysaccharide to oxymorphone hydrochloride is in the range of about 10:1 to about 1:10. A preferred heteropolysaccharide is xanthan gum and a preferred homopolysaccharide is locust bean gum. The dosage form also comprises a cationic cross-linking agent and a hydrophobic polymer. In the preferred embodiment, the dosage form is a tablet containing about 5 mg to about 80 mg of oxymorphone hydrochloride. In a most preferred embodiment, the tablet contains about 20 mg oxymorphone hydrochloride.

The invention includes a method which comprises achieving appropriate blood plasma levels of drug while providing extended pain relief by administering one to three times per day to a patient suffering moderate to severe, acute or chronic pain, an oxymorphone controlled release oral solid dosage form of the invention in an amount sufficient to alleviate the pain for a period of about 8 hours to about 24 hours. This type and intensity of pain is often associated with cancer, autoimmune diseases, infections, surgical and accidental traumas and osteoarthritis.

The invention also includes a method of making an oxymorphone controlled release oral solid dosage form of the invention which comprises mixing particles of oxymorphone or a pharmaceutically acceptable salt of oxymorphone with granules comprising the controlled release delivery system, preferably followed by directly compressing the mixture to form tablets.

Pharmaceutically acceptable salts of oxymorphone which can be used in this invention include salts with the inorganic and organic acids which are commonly used to produce non-toxic salts of medicinal agents. Illustrative examples would be those salts formed by mixing oxymorphone with hydrochloric, sulfuric, nitric, phosphoric, phosphorous, hydrobromic, maleric, malic, ascorbic, citric or tartaric, pamoic, lauric, stearic, palmitic, oleic, myristic, lauryl sulfuric, naphthylenesulfonic, linoleic or linolenic acid, and the like. The hydrochloride salt is preferred.

It has now been found that 6-OH oxymorphone, which is one of the metabolites of oxymorphone, may play a role in alleviating pain. When oxymorphone is ingested, part of the dosage gets into the bloodstream to provide pain relief, while another part is metabolized to 6-OH oxymorphone. This metabolite then enters the bloodstream to provide further pain relief. Thus it is believed that both the oxymorphone and 6-hydroxyoxymorphone levels are important to pain relief.

The effectiveness of oxymorphone and 6-hydroxyoxymorphone at relieving pain and the pharmacokinetics of a single dose of oxymorphone were studied. The blood plasma levels of both oxymorphone and 6-hydroxyoxymorphone were measured in patients after a single dose of oxymorphone was administered. Similarly, the pain levels in patients were measured after a single administration of oxymorphone to determine the effective duration of pain relief from a single dose. FIGS. 1-2 show the results of these tests, comparing pain levels to oxymorphone and 6-hydroxy oxymorphone levels.

For these tests, pain was measured using a Visual Analog Scale (VAS) or a Categorical Scale. The VAS scales consisted of a horizontal line, 100 mm in length. The left-hand end of the scale (0 mm) was marked with the descriptor "No Pain" and the right-hand end of the scale (100 mm) was marked with the descriptor "Extreme Pain". Patients indicated their level of pain by making a vertical mark on the line. The VAS score was equal to the distance (in mm) from the left-hand end of the scale to the patient's mark. For the categorical scale, patients completed the following statement, "My pain at this time is" using the scale None=0, Mild=1, Moderate=2, or Severe=3.

As can be seen from these figures, there is a correlation between pain relief and both oxymorphone and 6-hydroxyoxymorphone levels. As the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone increase, pain decreases (and pain intensity difference and pain relief increases). Thus, to the patient, it is the level of oxymorphone and 6-hydroxyoxymorphone in the blood plasma which is most important. Further it is these levels which dictate the efficacy of the dosage form. A dosage form which maintains a sufficiently high level of oxymorphone or 6-hydroxyoxymorphone for a longer period need not be administered frequently. Such a result is accomplished by embodiments of the present invention.

The oxymorphone controlled release oral solid dosage form of this invention can be made using any of several different techniques for producing controlled release oral solid dosage forms of opioid analgesics.

In one embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material and which upon exposure to gastrointestinal fluid releases oxymorphone from the core at a controlled rate. In a second embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. A third embodiment is a combination of the first two: a controlled release matrix coated with a controlled release film. In a fourth embodiment the oxymorphone is incorporated into an osmotic pump. In any of these embodiments, the dosage form can be a tablet, a plurality of granules in a capsule, or other suitable form, and can contain lubricants, colorants, diluents, and other conventional ingredients.

Osmotic Pump

An osmotic pump comprises a shell defining an interior compartment and having an outlet passing through the shell. The interior compartment contains the active pharmaceutical ingredient. Generally the active pharmaceutical ingredient is mixed with excipients or other compositions such as a polyalkylene. The shell is generally made, at least in part, from a material (such as cellulose acetate) permeable to the liquid of the environment where the pump will be used, usually stomach acid. Once ingested, the pump operates when liquid diffuses through the shell of the pump. The liquid dissolves the composition to produce a saturated situation. As more liquid diffuses into the pump, the saturated solution containing the pharmaceutical is expelled from the pump through the outlet. This produces a nearly constant release of active ingredient, in the present case, oxymorphone.

Controlled Release Coating

In this embodiment, a core comprising oxymorphone or oxymorphone salt is coated with a controlled release film which comprises a water insoluble material. The film can be applied by spraying an aqueous dispersion of the water insoluble material onto the core. Suitable water insoluble materials include alkyl celluloses, acrylic polymers, waxes (alone or in admixture with fatty alcohols), shellac and zein. The aqueous dispersions of alkyl celluloses and acrylic polymers preferably contain a plasticizer such as triethyl citrate, dibutyl phthalate, propylene glycol, and polyethylene glycol. The film coat can contain a water-soluble material such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC).

The core can be a granule made, for example, by wet granulation of mixed powders of oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by coating an inert bead with oxymorphone or oxymorphone salt and a binding agent such as HPMC, or by spheronising mixed powders of oxymorphone or oxymorphone salt and a spheronising agent such as microcrystalline cellulose. The core can be a tablet made by compressing such granules or by compressing a powder comprising oxymorphone or oxymorphone salt.

The in vitro and in vivo release characteristics of this controlled release dosage form can be modified by using mixtures of different water insoluble and water soluble materials, using different plasticizers, varying the thickness of the controlled release film, including release-modifying agents in the coating, or by providing passageways through the coating.

Controlled Release Matrix

It is important in the present invention that appropriate blood plasma levels of oxymorphone and 6-hydroxy oxymorphone be achieved and maintained for sufficient time to provide pain relief to a patient for a period of 12 to 24 hours. The preferred composition for achieving and maintaining the proper blood plasma levels is a controlled-release matrix. In this embodiment, the oxymorphone or oxymorphone salt is dispersed in a controlled release delivery system that comprises a hydrophilic material (gelling agent) which upon exposure to gastrointestinal fluid forms a gel matrix that releases oxymorphone at a controlled rate. Such hydrophilic materials include gums, cellulose ethers, acrylic resins, and protein-derived materials. Suitable cellulose ethers include hydroxyalkyl celluloses and carboxyalkyl celluloses, especially hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), HPMC, and carboxy methylcellulose (CMC). Suitable acrylic resins include polymers and copolymers of acrylic acid, methacrylic acid, methyl acrylate and methyl methacrylate. Suitable gums include heteropolysaccharide and homopolysaccharide gums, e.g., xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, and locust bean gums.

Preferably, the controlled release tablet of the present invention is formed from (I) a hydrophilic material comprising (a) a heteropolysaccharide; or (b) a heteropolysaccharide

and a cross-linking agent capable of cross-linking said heteropolysaccharide; or (c) a mixture of (a), (b) and a polysaccharide gum; and (II) an inert pharmaceutical filler comprising up to about 80% by weight of the tablet; and (III) oxymorphone.

The term "heteropolysaccharide" as used herein is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

A preferred heteropolysaccharide is xanthan gum, which is a high molecular weight (>10^6) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The cross linking agents used in the controlled release embodiment of the present invention which are capable of cross-linking with the heteropolysaccharide include homopolysaccharide gums such as the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to the galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

Preferably, the ratio of heteropolysaccharide to homopolysaccharide is in the range of about 1:9 to about 9:1, preferably about 1:3 to about 3:1. Most preferably, the ratio of xanthan gum to polysaccharide material (i.e., locust bean gum, etc.) is preferably about 1:1.

In addition to the hydrophilic material, the controlled release delivery system can also contain an inert pharmaceutical diluent such as a monosaccharide, a disaccharide, a polyhydric alcohol and mixtures thereof. The ratio of diluent to hydrophilic matrix-forming material is generally in the range of about 1:3 to about 3:1.

The controlled release properties of the controlled release embodiment of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80% or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropyl cellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert filler of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The cationic cross-linking agent which is optionally used in conjunction with the controlled release embodiment of the present invention may be monovalent or multivalent metal cations. The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Specific examples of suitable cationic cross-linking agents include calcium sulfate, sodium chloride, potassium sulfate, sodium carbonate, lithium chloride, tripotassium phosphate, sodium borate, potassium bromide, potassium fluoride, sodium bicarbonate, calcium chloride, magnesium chloride, sodium citrate, sodium acetate, calcium lactate, magnesium sulfate and sodium fluoride. Multivalent metal cations may also be utilized. However, the preferred cationic cross-linking agents are bivalent. Particularly preferred salts are calcium sulfate and sodium chloride. The cationic cross-linking agents of the present invention are added in an amount effective to obtain a desirable increased gel strength due to the cross-linking of the gelling agent (e.g., the heteropolysaccharide and homopolysaccharide gums). In preferred embodiments, the cationic cross-linking agent is included in the sustained release excipient of the present invention in an amount from about 1 to about 20% by weight of the sustained release excipient, and in an amount about 0.5% to about 16% by weight of the final dosage form.

In the controlled release embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99% by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum, from about 1 to about 20% by weight of a cationic crosslinking agent, and from about 0 to about 89% by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75% gelling agent, from about 2 to about 15% cationic crosslinking agent, and from about 30 to about 75% inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75% gelling agent, from about 5 to about 10% cationic cross-linking agent, and from about 15 to about 65% inert diluent.

The sustained release excipient used in this embodiment of the present invention (with or without the optional cationic cross-linking agent) may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic polymer may be selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incor-

porated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20% by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat coating (aqueous dispersion of ethylcellulose available from FMC of Philadelphia, Pa.) and Surelease coating (aqueous dispersion of ethylcellulose available from Colorcon of West Point, Pa.). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit RS and RL polymers (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds available from Rohm America of Piscataway, N.J.).

The controlled release matrix useful in the present invention may also contain a cationic cross-linking agent such as calcium sulfate in an amount sufficient to cross-link the gelling agent and increase the gel strength, and an inert hydrophobic material such as ethyl cellulose in an amount sufficient to slow the hydration of the hydrophilic material without disrupting it. Preferably, the controlled release delivery system is prepared as a pre-manufactured granulation.

EXAMPLES

Example 1

Two controlled release delivery systems are prepared by dry blending xanthan gum, locust bean gum, calcium sulfate dehydrate, and dextrose in a high speed mixed/granulator for 3 minutes. A slurry is prepared by mixing ethyl cellulose with alcohol. While running choppers/impellers, the slurry is added to the dry blended mixture, and granulated for another 3 minutes. The granulation is then dried to a LOD (loss on drying) of less than about 10% by weight. The granulation is then milled using 20 mesh screen. The relative quantities of the ingredients are listed in the table below.

TABLE 1

Controlled Release Delivery System

Excipient	Formulation 1 (%)	Formulation 2 (%)
Locust Bean Gum, FCC	25.0	30.0
Xanthan Gum, NF	25.0	30.0
Dextrose, USP	35.0	40.0
Calcium Sulfate Dihydrate, NF	10.0	0.0
Ethylcellulose, NF	5.0	0.0
Alcohol, SD3A (Anhydrous)	(10)[1]	(20.0)[1]
Total	100.0	100.0

A series of tablets containing different amounts of oxymorphone hydrochloride were prepared using the controlled release delivery Formulation 1 shown in Table 1. The quantities of ingredients per tablet are as listed in the following table.

TABLE 2

Sample Tablets of Differing Strengths

Component	Amounts in Tablet (mg)				
Oxymorphone HCl, USP (mg)	5	10	20	40	80
Controlled release delivery system	160	160	160	160	160
Silicified microcrystalline cellulose, N.F.	20	20	20	20	20
Sodium stearyl fumarate, NF	2	2	2	2	2
Total weight	187	192	202	222	262
Opadry (colored)	7.48	7.68	8.08	8.88	10.48
Opadry (clear)	0.94	0.96	1.01	1.11	1.31

Examples 2 and 3

Two batches of 20 mg tablets were prepared as described above, using the controlled release delivery system of Formulation 1. One batch was formulated to provide relatively fast controlled release, the other batch was formulated to provide relatively slow controlled release. Compositions of the tablets are shown in the following table.

TABLE 3

Slow and Fast Release Compositions

Ingredients	Example 2 Slow (mg)	Example 3 Fast (mg)	Example 4 Fast (mg)
Oxymorphone HCl, USP	20	20	20
Controlled Release Delivery System	360	160	160
Silicified Microcrystalline Cellulose, NF	20	20	20
Sodium stearyl fumarate, NF	4	2	2
Total weight	404	202	202
Coating (color or clear)	12	12	9

The tablets of Examples 2, 3, and 4 were tested for in vitro release rate according to USP Procedure Drug Release U.S. Pat. No. 23. Release rate is a critical variable in attempting to control the blood plasma levels of oxymorphone and 6-hydroxyoxymorphone in a patient. Results are shown in the following Table 4.

TABLE 4

Release Rates of Slow and Fast Release Tablets

Time (hr)	Example 2 (Slow Release)	Example 3 (Fast Release)	Example 4 (Fast Release)
0.5	18.8	21.3	20.1
1	27.8	32.3	31.7
2	40.5	47.4	46.9
3	50.2	58.5	57.9
4	58.1	66.9	66.3
5	64.7	73.5	74.0
6	70.2	78.6	83.1
8	79.0	86.0	92.0
10	85.3	90.6	95.8
12	89.8	93.4	97.3

Clinical Studies

Three clinical studies were conducted to assess the bioavailability (rate and extent of absorption) of oxymorphone. Study 1 addressed the relative rates of absorption of con-

trolled release (CR) oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fasted patients. Study 2 addressed the relative rates of absorption of CR oxymorphone tablets (of Examples 2 and 3) and oral oxymorphone solution in fed patients. Study 3 addressed the relative rates of absorption of CR oxymorphone tablets (of Example 4) and oral oxymorphone solution in fed and fasted patients.

The blood plasma levels set forth herein as appropriate to achieve the objects of the present invention are mean blood plasma levels. As an example, if the blood plasma level of oxymorphone in a patient 12 hours after administration of a tablet is said to be at least 0.5 ng/ml, any particular individual may have lower blood plasma levels after 12 hours. However, the mean minimum concentration should meet the limitation set forth. To determine mean parameters, a study should be performed with a minimum of 8 adult subjects, in a manner acceptable for filing an application for drug approval with the US Food and Drug Administration. In cases where large fluctuations are found among patients, further testing may be necessary to accurately determine mean values.

For all studies, the following procedures were followed, unless otherwise specified for a particular study.

The subjects were not to consume any alcohol-, caffeine-, or xanthine-containing foods or beverages for 24 hours prior to receiving study medication for each study period. Subjects were to be nicotine and tobacco free for at least 6 months prior to enrolling in the study. In addition, over-the-counter medications were prohibited 7 days prior to dosing and during the study. Prescription medications were not allowed 14 days prior to dosing and during the study.

Pharmacokinetic and Statistical Methods

The following pharmacokinetic parameters were computed from the plasma oxymorphone concentration-time data:

$AUC_{(0-t)}$ Area under the drug concentration-time curve from time zero to the time of the last quantifiable concentration (Ct), calculated using linear trapezoidal summation.

$AUC_{(0-inf)}$ Area under the drug concentration-time curve from time zero to infinity. $AUC_{(0-inf)}=AUC_{(0-t)}+Ct/K_{el}$, where K_{el} is the terminal elimination rate constant.

$AUC_{(0-24)}$ Partial area under the drug concentration-time curve from time zero to 24 hours.

C_{max} Maximum observed drug concentration.

T_{max} Time of the observed maximum drug concentration.

K_{el} Elimination rate constant based on the linear regression of the terminal linear portion of the LN (concentration) time curve.

Terminal elimination rate constants for use in the above calculations were in turn computed using linear regression of a minimum of three time points, at least two of which were consecutive. K_{el} values for which correlation coefficients were less than or equal to 0.8 were not reported in the pharmacokinetic parameter tables or included in the statistical analysis. Thus $AUC_{(0-inf)}$ was also not reported in these cases.

A parametric (normal-theory) general linear model was applied to each of the above parameters (excluding T_{max}), and the LN-transformed parameters C_{max}, $AUC_{(0-24)}$, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. Initially, the analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period, and carryover effect. If carryover effect was not significant, it was dropped from the model. The sequence effect was tested using the subject within sequence mean square, and all other main effects were tested using the residual error (error mean square).

Plasma oxymorphone concentrations were listed by subject at each collection time and summarized using descriptive statistics. Pharmacokinetic parameters were also listed by subject and summarized using descriptive statistics.

Study 1-Two Controlled Release Formulations; Fasted Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water after a 10-hour fast. Subjects received the tablets of Example 2 (Treatment 1A) or Example 3 (Treatment 1B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 1C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. Subjects were in a fasted state following a 10-hour overnight fast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 1C were confined for 18 hours and subjects receiving Treatments 1A or 1B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 1A or 1B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours post-dose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 5.

TABLE 5

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 1A	Treatment 1B	Treatment 1C
0	0.000	0.000	0.0000
0.25			0.9489
0.5	0.2941	0.4104	1.3016
0.75			1.3264
1	0.5016	0.7334	1.3046
1.25			1.2041
1.5	0.5951	0.8192	1.0813
1.75			0.9502
2	0.6328	0.7689	0.9055
2.5			0.7161
3	0.5743	0.7341	0.6689
4	0.5709	0.6647	0.4879
5	0.7656	0.9089	0.4184
6	0.7149	0.7782	0.3658
7	0.6334	0.6748	0.3464
8	0.5716	0.5890	0.2610
10	0.4834	0.5144	0.2028
12	0.7333	0.6801	0.2936
14	0.6271	0.6089	0.2083
16	0.4986	0.4567	0.1661
18	0.4008	0.3674	0.1368
20	0.3405	0.2970	
24	0.2736	0.2270	
28	0.3209	0.2805	
32	0.2846	0.2272	
36	0.2583	0.1903	
48	0.0975	0.0792	

The results are shown graphically in FIG. 5. In both Table 5 and FIG. 5, the results are normalized to a 20 mg dosage. The immediate release liquid of Treatment 1C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration. However, the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. The first peak occurs (on average) at around 3 hours. The second peak of the mean blood plasma concentration is higher than the first, occurring around 6-7 hours, on average).

Occasionally, in an individual, the first peak is higher than the second, although generally this is not the case. This makes it difficult to determine the time to maximum blood plasma concentration (T_{max}) because if the first peak is higher than the second, maximum blood plasma concentration (C_{max}) occurs much earlier (at around 3 hours) than in the usual case where the second peak is highest. Therefore, when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak. Further, when reference is made to the second peak, we refer to the time or blood plasma concentration at the point where the blood plasma concentration begins to drop the second time. Generally, where the first peak is higher than the second, the difference in the maximum blood plasma concentration at the two peaks is small. Therefore, this difference (if any) was ignored and the reported C_{max} was the true maximum blood plasma concentration and not the concentration at the second peak.

TABLE 6

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 1

	Treatment 1A		Treatment 1B		Treatment 1C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	0.8956	0.2983	1.0362	0.3080	2.9622	1.0999
T_{max}	7.03	4.10	4.89	3.44	0.928	0.398
$AUC_{(0-t)}$	17.87	6.140	17.16	6.395	14.24	5.003
$AUC_{(0-inf)}$	19.87	6.382	18.96	6.908	16.99	5.830
$T_{1/2el}$	10.9	2.68	11.4	2.88	6.96	4.61

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

Relative bioavailability determinations are set forth in Tables 7 and 8. For these calculations, AUC was normalized for all treatments to a 20 mg dose.

TABLE 7

Relative Bioavailability (F_{rel}) Determination Based on $AUC_{(0-inf)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
1.193 .±. 0.203	1.121 .±. 0.211	1.108 .±. 0.152

TABLE 8

Relative Bioavailability Determination Based on $AUC_{(0-18)}$

F_{rel} (1A vs. 1C)	F_{rel} (1B vs. 1C)	F_{rel} (1A vs. 1B)
0.733 .±. 0.098	0.783 .±. 0.117	0.944 .±. 0.110

Study 2-Two CR Formulations; Fed Patients

Healthy volunteers received a single oral dose of 20 mg CR oxymorphone taken with 240 ml water in a fed state. Subjects received the tablets of Example 2 (Treatment 2A) or Example 3 (Treatment 2B). Further subjects were given a single oral dose of 10 mg/10 ml oxymorphone solution in 180 ml apple juice followed with 60 ml water (Treatment 2C). The orally dosed solution was used to simulate an immediate release (IR) dose.

This study had a single-center, open-label, randomized, three-way crossover design using fifteen subjects. The subjects were in a fed state, after a 10-hour overnight fast followed by a standardized FDA high-fat breakfast. There was a 14-day washout interval between the three dose administrations. The subjects were confined to the clinic during each study period. Subjects receiving Treatment 2C were confined for 18 hours and subjects receiving Treatments 2A or 2B were confined for 48 hours after dosing. Ten-milliliter blood samples were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, and 48 hours postdose for subjects receiving Treatment 2A or 2B and 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 18 hours postdose. The mean plasma concentration of oxymorphone versus time for each treatment across all subjects is shown in table 9.

TABLE 9

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 2A	Treatment 2B	Treatment 2C
0	0.000	0.000	0.0000
0.25			1.263
0.5	0.396	.0553	1.556
0.75			1.972
1	0.800	1.063	1.796
1.25			1.795
1.5	1.038	1.319	1.637
1.75			1.467
2	1.269	1.414	1.454
2.5			1.331
3	1.328	1.540	1.320
4	1.132	1.378	1.011
5	1.291	1.609	0.731
6	1.033	1.242	0.518
7	0.941	0.955	0.442
8	0.936	0.817	0.372
10	0.669	0.555	0.323
12	0.766	0.592	0.398
14	0.641	0.519	0.284
16	0.547	0.407	0.223
18	0.453	0.320	0.173
20	0.382	0.280	
24	0.315	0.254	
28	0.352	0.319	
32	0.304	0.237	
36	0.252	0.207	
48	0.104	0.077	

The results are shown graphically in FIG. 6. Again, the results have been normalized to a 20 mg dosage. As with Study 1, the immediate release liquid of Treatment 2C shows a classical curve, with a high and relatively narrow peak, followed by an exponential drop in plasma concentration, while the controlled release oxymorphone tablets exhibit triple peaks in blood plasma concentration. Thus, again when we refer to the time to peak plasma concentration (T_{max}) unless otherwise specified, we refer to the time to the second peak.

TABLE 10

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.644	0.365	1.944	0.465	4.134	0.897
T_{max}	3.07	1.58	2.93	1.64	0.947	0.313
$AUC_{(0-t)}$	22.89	5.486	21.34	5.528	21.93	5.044

TABLE 10-continued

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 2

	Treatment 2A		Treatment 2B		Treatment 2C	
	Mean	SD	Mean	SD	Mean	SD
$AUC_{(0\text{-}inf)}$	25.28	5.736	23.62	5.202	24.73	6.616
$T_{1/2el}$	12.8	3.87	11.0	3.51	5.01	2.02

Units:
C_{max} in ng/ml,
T_{max} in hours,
AUC in ng * hr/ml,
$T_{1/2el}$ in hours.

In Table 10, the T_{max} has a large standard deviation due to the two comparable peaks in blood plasma concentration. Relative bioavailability determinations are set forth in Tables 11 and 12.

TABLE 11

Relative Bioavailability Determination Based on $AUC_{(0\text{-}inf)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
1.052 .±. 0.187	0.949 .±. 0.154	1.148 .±. 0.250

TABLE 12

Relative bioavailability Determination Based on $AUC_{(0\text{-}12)}$

F_{rel} (2A vs. 2C)	F_{rel} (2B vs. 2C)	F_{rel} (2A vs. 2B)
0.690 .±. 0.105	0.694 .±. 0.124	1.012 .±. 0.175

As may be seen from tables 5 and 10 and FIGS. 1 and 2, the C_{max} for the CR tablets (treatments 1A, 1B, 2A and 2B) is considerably lower, and the T_{max} much higher than for the immediate release oxymorphone. The blood plasma level of oxymorphone remains high well past the 8 (or even the 12) hour dosing interval desired for an effective controlled release tablet.

Study 3-One Controlled Release Formulation; Fed and Fasted Patients

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 3A and Treatment 3C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 3B and Treatment 3D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subjects assigned to receive Treatment 3A and Treatment 3B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 3C and Treatment 3D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 3A and 3B: Oxymorphone controlled release 20 mg tablets from Example 3. Subjects randomized to Treatment 3A received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3B received a single oral dose of one 20 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 3C and 3D: oxymorphone HCl solution, USP, 1.5 mg/ml 10 ml vials. Subjects randomized to Treatment 3C received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 3D received a single oral dose of 10 mg (6.7 ml) oxymorphone solution taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 24 subjects completed the study. The mean age of the subjects was 27 years (range of 19 through 38 years), the mean height of the subjects was 69.6 inches (range of 64.0 through 75.0 inches), and the mean weight of the subjects was 169.0 pounds (range 117.0 through 202.0 pounds).

A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post-dose (19 samples) for subjects randomized to Treatment 3A and Treatment 3B. Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, and 36 hours post-dose (21 samples) for subjects randomized to Treatment 3C and Treatment 3D.

The mean oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 7. The results have been normalized to a 20 mg dosage. The data is contained in Table 13. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 14.

TABLE 13

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0084	0.0309	0.0558	0.0000
0.25			0.5074	0.9905
0.5	0.3853	0.3380	0.9634	1.0392
0.75			0.9753	1.3089
1	0.7710	0.7428	0.8777	1.3150
1.25			0.8171	1.2274
1.5	0.7931	1.0558	0.7109	1.1638
1.75			0.6357	1.0428
2	0.7370	1.0591	0.5851	0.9424
3	0.6879	0.9858	0.4991	0.7924
4	0.6491	0.9171	0.3830	0.7277
5	0.9312	1.4633	0.3111	0.6512
6	0.7613	1.0441	0.2650	0.4625
8	0.5259	0.7228	0.2038	0.2895
10	0.4161	0.5934	0.1768	0.2470
12	0.5212	0.5320	0.2275	0.2660
14	0.4527	0.4562	0.2081	0.2093
16	0.3924	0.3712	0.1747	0.1623
20	0.2736	0.3021	0.1246	0.1144
24	0.2966	0.2636	0.1022	0.1065
30	0.3460	0.3231		
36	0.2728	0.2456	0.0841	0.0743
48	0.1263	0.1241		

TABLE 14

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3B		Treatment 3A		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.7895	0.6531	1.1410	0.4537	2.2635	1.0008	3.2733	1.3169
T_{max}	5.65	9.39	5.57	7.14	0.978	1.14	1.11	0.768
$AUC_{(0-24)}$	14.27	4.976	11.64	3.869	12.39	4.116	17.30	5.259
$AUC_{(0-t)}$	19.89	6.408	17.71	8.471	14.53	4.909	19.20	6.030
$AUC_{(0-inf)}$	21.29	6.559	19.29	5.028	18.70	6.618	25.86	10.03
$T_{1/2el}$	12.0	3.64	12.3	3.99	16.2	11.4	20.6	19.3

The relative bioavailability calculations are summarized in tables 15 and 16.

TABLE 15

Relative Bioavailability Determination Based on $AUC_{(0-inf)}$

F_{rel} (3A vs. 3C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
1.040 .±. 0.1874	0.8863 .±. 0.2569	1.368 .±. 0.4328	1.169 .±. 0.2041

TABLE 16

Relative bioavailability Determination Based on $AUC_{(0-24)}$

F_{rel} (3A vs. 2C)	F_{rel} (3B vs. 3D)	F_{rel} (3D vs. 3C)	F_{rel} (3A vs. 3B)
0.9598 .±. 0.2151	0.8344 .±. 0.100	1.470 .±. 0.3922	1.299 .±. 0.4638

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (20 mg) compared to oxymorphone oral solution (10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the oral solution.

The presence of a high fat meal had a substantial effect on the oxymorphone C_{max}, but less of an effect on oxymorphone AUC from oxymorphone controlled release tablets. Least Squares (LS) mean C_{max} was 58% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 18% higher for the fed condition (Treatment B) compared to the fasted condition (Treatment A) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.17. Mean T_{max} values were similar (approximately 5.6 hours), and no significant difference in T_{max} was shown using nonparametric analysis. Half value durations were significantly different between the two treatments.

The effect of food on oxymorphone bioavailability from the oral solution was more pronounced, particularly in terms of AUC. LS mean C_{max} was 50% higher and LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were 32-34% higher for the fed condition (Treatment D) compared to the fasted condition (Treatment C) based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-inf)}$ since mean F_{rel} was 1.37. Mean T_{max} (approximately 1 hour) was similar for the two treatments and no significant difference was shown.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar extent of oxymorphone availability compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 17% higher for oxymorphone CR, whereas LS mean $AUC_{(0-inf)}$ values were nearly equal (mean ratio=99%). Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (1.0 and 0.96, respectively) also showed similar extent of oxymorphone availability between the two treatments.

As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 49% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Half-value duration was significantly longer for the controlled release formulation (means, 12 hours versus 2.5 hours).

Under fed conditions, oxymorphone availability from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-inf)}$ was 12% lower for oxymorphone CR. Mean F_{rel} values calculated from $AUC_{(0-inf)}$ and $AUC_{(0-24)}$, (0.89 and 0.83 respectively) also showed similar extent of oxymorphone availability from the tablet. As expected, there were differences in parameters reflecting rate of absorption. LS mean C_{max} was 46% lower for oxymorphone controlled release tablets compared to the dose-normalized oral solution, based on LN-transformed data. Mean T_{max} was 5.7 hours for the tablet compared to 1.1 hours for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 7.8 hours versus 3.1 hours).

The presence of a high fat meal did not appear to substantially affect the availability of 6-hydroxymorphone following administration of oxymorphone controlled release tablets. LS mean ratios were 97% for $AUC_{(0-t)}$ and 91% for C_{max} (Treatment B versus A), based on LN-transformed data. This was consistent with the relative bioavailability determination from $AUC_{(0-24)}$, since mean F_{rel} was 0.97. Mean T_{max}, was

later for the fed treatment compared to the fasted treatment (5.2 and 3.6 hours, respectively), and difference was significant.

Under fasted conditions, oxymorphone controlled release 20 mg tablets exhibited similar availability of 6-hydroxymorphone compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment A versus Treatment C). From LN-transformed data, LS mean ratio for $AUC_{(0-t)}$ was 104.5%. Mean F_{rel} (0.83) calculated from $AUC_{(0-24)}$ also showed similar extent of oxymorphone availability between the two treatments. Mean T_{max} was 3.6 hours for the tablet compared to 0.88 for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 11 hours versus 2.2 hours).

Under fed conditions, availability of 6-hydroxymorphone from oxymorphone controlled release 20 mg was similar compared to 10 mg oxymorphone oral solution normalized to a 20 mg dose (Treatment B versus Treatment D). From LN-transformed data, LS mean $AUC_{(0-t)}$ was 14% higher for oxymorphone CR. Mean F_{rel} (0.87) calculated from $AUC_{(0-24)}$ also indicated similar extent of availability between the treatments. Mean T_{max} was 5.2 hours for the tablet compared to 1.3 hour for the oral solution. Half-value duration was significantly longer for the controlled release formulation (means, 14 hours versus 3.9 hours).

The extent of oxymorphone availability from oxymorphone controlled release 20 mg tablets was similar under fed and fasted conditions since there was less than a 20% difference in LS mean $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ values for each treatment, based on LN-transformed data. T_{max} was unaffected by food; however, LS mean C_{max} was increased 58% in the presence of the high fat meal. Both rate and extent of oxymorphone absorption from the oxymorphone oral solution were affected by food since LS mean C_{max} and AUC values were increased approximately 50 and 30%, respectively. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of oxymorphone availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC(0-t) and AUC(0-inf) values for each treatment.

Bioavailability of 6-hydroxymorphone following oxymorphone controlled release 20 mg tablets was also similar under fed and fasted conditions since there was less than a 20% difference in LS mean C_{max} and AUC values for each treatment. T_{max} was later for the fed condition. The presence of food did not affect the extent of availability from oxymorphone oral solution since LS mean AUC values were less than 20% different. However, C_{max} was decreased 35% in the presence of food. T_{max} was unaffected by food. Under both fed and fasted conditions, oxymorphone controlled release tablets exhibited similar extent of availability compared to oxymorphone oral solution since there was less than a 20% difference in LS mean AUC values for each treatment.

The mean 6-OH oxymorphone plasma concentration versus time curves for Treatments 3A, 3B, 3C, and 3D are presented in FIG. 8. The data is contained in Table 17.

TABLE 17

Mean Plasma Concentration vs. Time (ng/ml) 6-Hydroxyoxymorphone

Time (hr)	Treatment 3A	Treatment 3B	Treatment 3C	Treatment 3D
0	0.0069	0.0125	0.0741	0.0000
0.25			0.7258	0.4918
0.5	0.5080	0.1879	1.2933	0.5972
0.75			1.3217	0.7877
1	1.0233	0.4830	1.1072	0.8080
1.25			1.0069	0.7266
1.5	1.1062	0.7456	0.8494	0.7001
1.75			0.7511	0.6472
2	1.0351	0.7898	0.6554	0.5758
3	0.9143	0.7619	0.6196	0.5319
4	0.8522	0.7607	0.4822	0.5013
5	0.8848	0.8548	0.3875	0.4448
6	0.7101	0.7006	0.3160	0.3451
8	0.5421	0.5681	0.2525	0.2616
10	0.4770	0.5262	0.2361	0.2600
12	0.4509	0.4454	0.2329	0.2431
14	0.4190	0.4399	0.2411	0.2113
16	0.4321	0.4230	0.2385	0.2086
20	0.3956	0.4240	0.2234	0.1984
24	0.4526	0.4482	0.2210	0.2135
30	0.4499	0.4708		
36	0.3587	0.3697	0.1834	0.1672
48	0.3023	0.3279		

TABLE 18

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 3

	Treatment 3A		Treatment 3B		Treatment 3C		Treatment 3D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.2687	0.5792	1.1559	0.4848	1.5139	0.7616	0.9748	0.5160
T_{max}	3.61	7.17	5.20	9.52	0.880	0.738	1.30	1.04
$AUC_{(0-t)}$	22.47	10.16	22.01	10.77	10.52	4.117	9.550	4.281
$AUC_{(0-inf)}$	38.39	23.02	42.37	31.57	20.50	7.988	23.84	11.37
$T_{1/2el}$	39.1	36.9	39.8	32.6	29.3	12.0	44.0	35.00

Study 4-Controlled Release 20 mg vs Immediate Release 10 mg

A study was conducted to compare the bioavailability and pharmacokinetics of controlled release and immediate release oxymorphone tablets under single-dose and multiple-dose (steady state) conditions. For the controlled release study, healthy volunteers received a single dose of a 20 mg

controlled release oxymorphone table on the morning of Day 1. Beginning on the morning of Day 3, the volunteers were administered a 20 mg controlled release oxymorphone tablet every 12 hours through the morning dose of Day 9. For the immediate release study, healthy volunteers received a single 10 mg dose of an immediate release oxymorphone tablet on the morning of Day 1. On the morning of Day 3, additional 10 mg immediate release tablets were administered every six hours through the first two doses on Day 9.

FIG. **9** shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects after a single dose either controlled release (CR) 20 mg or immediate release (IR) 10 mg oxymorphone. The data in the figure (as with the other relative experimental data herein) is normalized to a 20 mg dose. The immediate release tablet shows a classical curve, with a high, relatively narrow peak followed by an exponential drop in plasma concentration. The controlled release oxymorphone tablets show a lower peak with extended moderate levels of oxymorphone and 6-hydroxy oxymorphone. Table 19 shows the levels of oxymorphone and 6-hydroxy oxymorphone from FIG. **9** in tabular form.

TABLE 19

Mean Plasma Concentration (ng/ml)

	Oxymorphone		6-Hydroxyoxymorphone	
Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
0.00	0.00	0.00	0.00	0.00
0.25	0.22	1.08	0.14	0.73
0.50	0.59	1.69	0.45	1.22
1.00	0.77	1.19	0.53	0.79
1.50	0.84	0.91	0.53	0.57
2.00	0.87	0.75	0.60	0.47
3.00	0.83	0.52	0.55	0.34
4.00	0.73	0.37	0.53	0.27
5.00	0.94	0.36	0.46	0.23
6.00	0.81	0.28	0.41	0.18
8.00	0.73	0.20	0.37	0.14
10.0	0.60	0.19	0.35	0.15
12.0	0.67	0.25	0.32	0.13
16.0	0.39	0.16	0.29	0.13
24.0	0.23	0.07	0.29	0.13
30.0	0.12	0.01	0.17	0.04
36.0	0.05	0.00	0.11	0.00
48.0	0.00	0.00	0.07	0.01

FIG. **10** shows the average plasma concentrations of oxymorphone and 6-hydroxyoxymorphone for all subjects in the steady state test, for doses of controlled release 20 mg tablets and immediate release 10 mg tablets of oxymorphone. The figure shows the plasma concentrations after the final controlled release tablet is given on Day 9, and the final immediate release tablet is given 12 hours thereafter. The steady state administration of the controlled release tablets clearly shows a steady moderate level of oxymorphone ranging from just over 1 ng/ml to almost 1.75 ng/ml over the course of a twelve hour period, where the immediate release tablet shows wide variations in blood plasma concentration. Table 20 shows the levels of oxymorphone and 6-hydroxyoxymorphone from FIG. **10** in tabular form.

TABLE 20

Summary of Mean Plasma Concentration (ng/ml)

		Oxymorphone		6-Hydroxyoxymorphone	
Day	Hour	Controlled Release 20 mg	Immediate Release 10 mg	Controlled Release 20 mg	Immediate Release 10 mg
4	0.00	1.10	0.75	0.89	0.72
5	0.00	1.12	0.84	1.15	0.88
6	0.00	1.20	0.92	1.15	0.87
7	0.00	1.19	0.91	1.27	1.00
8	0.00	1.19	0.86	1.29	0.98
9	0.00	1.03	1.07	1.09	1.05
	0.25		2.64		1.70
	0.50		3.12	1.50	2.09
	1.00		2.47	1.70	1.68
	1.50		2.05	1.63	1.55
	2.00		1.78	1.64	1.30
	3.00		1.27	1.47	1.11
	4.00		0.98	1.39	0.98
	5.00		1.01	1.21	0.89
	6.00		0.90	1.06	0.84
	6.25		1.17		0.88
	6.50		1.88		1.06
	7.00		2.12		1.20
	7.50		2.24		1.15
	8.00	1.32	2.01	0.97	1.03
	9.00		1.52		0.90
	10.0	1.32	1.24	0.85	0.84
	11.0		1.11		0.74
	12.0	1.18	0.96	0.79	0.70

TABLE 21

Mean Single-Dose Pharmacokinetic Results

	Controlled Release 20 mg		Immediate Release 10 mg	
	oxymorphone	6-OH-oxymorphone	oxymorphone	6-OH-oxymorphone
$AUC_{(o-t)}$	14.74	11.54	7.10	5.66
$AUC_{(o-inf)}$	15.33	16.40	7.73	8.45
C_{max}(ng/ml)	1.12	0.68	1.98	1.40
T_{max}(hr)	5.00	2.00	0.50	0.50
T½(hr)	9.25	26.09	10.29	29.48

Parent 6-OH oxymorphone $AUC_{(0-t)}$ values were lower than the parent compound after administration of either dosage form, but the $AUC_{(0-inf)}$ values are slightly higher due to the longer half-life for the metabolite. This relationship was similar for both the immediate-release (IR) and controlled release (CR) dosage forms. As represented by the average plasma concentration graph, the CR dosage form has a significantly longer time to peak oxymorphone concentration and a lower peak oxymorphone concentration. The 6-OH oxymorphone peak occurred sooner than the parent peak following the CR dosage form, and simultaneously with the parent peak following the IR dosage form.

It is important to note that while the present invention is described and exemplified using 20 mg tablets, the invention may also be used with other strengths of tablets. In each strength, it is important to note how a 20 mg tablet of the same composition (except for the change in strength) would act. The blood plasma levels and pain intensity information are provided for 20 mg tablets, however the present invention is also intended to encompass 5 to 80 mg controlled release tablets. For this reason, the blood plasma level of oxymorphone or 6-hydroxyoxymorphone in nanograms per milliliter of blood, per mg oxymorphone (ng/mg·ml) administered is measured. Thus at 0.02 ng/mg·ml, a 5 mg tablet should produce a minimum blood plasma concentration of 0.1 ng/ml. A stronger tablet will produce a higher blood plasma concentration of active molecule, generally proportionally. Upon administration of a higher dose tablet, for example 80 mg, the blood plasma level of oxymorphone and 6-OH oxymorphone may more than quadruple compared to a 20 mg dose, although conventional treatment of low bioavailability substances would lead away from this conclusion. If this is the case, it may be because the body can only process a limited amount oxymorphone at one time. Once the bolus is processed, the blood level of oxymorphone returns to a proportional level.

It is the knowledge that controlled release oxymorphone tablets are possible to produce and effective to use, which is most important, made possible with the high bioavailability of oxymorphone in a controlled release tablet. This also holds true for continuous periodic administration of controlled release formulations. The intent of a controlled release opioid formulation is the long-term management of pain. Therefore, the performance of a composition when administered periodically (one to three times per day) over several days is important. In such a regime, the patient reaches a "steady state" where continued administration will produce the same results, when measured by duration of pain relief and blood plasma levels of pharmaceutical. Such a test is referred to as a "steady state" test and may require periodic administration over an extended time period ranging from several days to a week or more. Of course, since a patient reaches steady state in such a test, continuing the test for a longer time period should not affect the results. Further, when testing blood plasma levels in such a test, if the time period for testing exceeds the interval between doses, it is important the regimen be stopped after the test is begun so that observations of change in blood level and pain relief may be made without a further dose affecting these parameters.

Study 5-Controlled Release 40 mg vs Immediate Release 4.Times.10 mg under Fed and Fasting Conditions

The objectives of this study were to assess the relative bioavailability of oxymorphone from oxymorphone controlled release (40 mg) compared to oxymorphone immediate release (4.times.10 mg) under both fasted and fed conditions, and to determine the effect of food on the bioavailability of oxymorphone from the controlled release formulation, oxymorphone CR, and from the immediate release formulation, oxymorphone IR.

This study had a single-center, open-label, analytically blinded, randomized, four-way crossover design. Subjects randomized to Treatment 5A and Treatment 5C, as described below, were in a fasted state following a 10-hour overnight fast. Subjects randomized to Treatment 5B and Treatment 5D, as described below, were in the fed state, having had a high fat meal, completed ten minutes prior to dosing. There was a 14-day washout interval between the four dose administrations. The subjects were confined to the clinic during each study period. Subject assigned to receive Treatment 5A and Treatment 5B were discharged from the clinic on Day 3 following the 48-hour procedures, and subjects assigned to receive Treatment 5C and Treatment 5D were discharged from the clinic on Day 2 following the 36-hour procedures. On Day 1 of each study period the subjects received one of four treatments:

Treatments 5A and 5B: Oxymorphone controlled release 40 mg tablets from Table 2. Subjects randomized to Treatment 5A received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5B received a single oral dose of one 40 mg oxymorphone controlled release tablet taken with 240 ml of water 10 minutes after a standardized high fat meal.

Treatments 5C and 5D: Immediate release tablet (IR) 4.times.10 mg Oxymorphone. Subjects randomized to Treatment 5C received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water after a 10-hour fasting period. Subjects randomized to Treatment 5D received a single oral dose of 4.times.10 mg oxymorphone IR tablet taken with 240 ml of water 10 minutes after a standardized high-fat meal.

A total of 28 male subjects were enrolled in the study, and 25 subjects completed the study. A total of 28 subjects received at least one treatment. Only subjects who completed all 4 treatments were included in the summary statistics and statistical analysis.

Blood samples (7 ml) were collected during each study period at the 0 hour (predose), and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours post-dose (19 samples) for subjects randomized to all Treatments.

The mean oxymorphone plasma concentration versus time is presented in Table 22. The arithmetic means of the plasma oxymorphone pharmacokinetic parameters and the statistics for all Treatments are summarized in Table 23.

TABLE 22

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.47	0.22	3.34	1.79
0.50	1.68	0.97	7.28	6.59
0.75	1.92	1.90	6.60	9.49
1	2.09	2.61	6.03	9.91
1.5	2.18	3.48	4.67	8.76
2	2.18	3.65	3.68	7.29
3	2.00	2.86	2.34	4.93
4	1.78	2.45	1.65	3.11
5	1.86	2.37	1.48	2.19
6	1.67	2.02	1.28	1.71
8	1.25	1.46	0.92	1.28
10	1.11	1.17	0.78	1.09
12	1.34	1.21	1.04	1.24

TABLE 22-continued

Mean Plasma Concentration vs. Time (ng/ml)

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
24	0.55	0.47	0.40	0.44
36	0.21	0.20	0.16	0.18
48	0.06	0.05	0.04	0.05
60	0.03	0.01	0.01	0.01
72	0.00	0.00	0.00	0.00

TABLE 23

Pharmacokinetic Parameters of Plasma Oxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	2.79	0.84	4.25	1.21	9.07	4.09	12.09	5.42
T_{max}	2.26	2.52	1.96	1.06	0.69	0.43	1.19	0.62
$AUC_{(0-t)}$	35.70	10.58	38.20	11.04	36.00	12.52	51.35	20.20
$AUC_{(0-inf)}$	40.62	11.38	41.17	10.46	39.04	12.44	54.10	20.26
$T_{1/2el}$	12.17	7.57	10.46	5.45	11.65	6.18	9.58	3.63

The relative bioavailability calculations are summarized in Tables 24 and 25.

TABLE 24

Relative Bioavailability Determination Based on $AUC_{(t=inf)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.3775	1.0220

TABLE 25

Relative bioavailability Determination Based on $AUC_{(t=24)}$

F_{rel} (5D vs. 5C)	F_{rel} (5B vs. 5A)
1.4681	1.0989

The mean 6-OH oxymorphone plasma concentration versus time is presented in Table 26.

TABLE 26

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
0	0.00	0.00	0.00	0.00
0.25	0.27	0.05	2.36	0.50
0.50	1.32	0.31	5.35	1.98
0.75	1.37	0.59	4.53	2.97
1	1.44	0.82	3.81	2.87
1.5	1.46	1.09	2.93	2.58
2	1.46	1.28	2.37	2.29
3	1.39	1.14	1.69	1.72
4	1.25	1.14	1.33	1.26
5	1.02	1.00	1.14	1.01
6	0.93	0.86	0.94	0.86
8	0.69	0.72	0.73	0.77
10	0.68	0.67	0.66	0.75
12	0.74	0.66	0.70	0.77
24	0.55	0.52	0.54	0.61
36	0.23	0.30	0.28	0.27

TABLE 26-continued

Mean Plasma Concentration vs. Time (ng/ml)
6-Hydroxyoxymorphone

Time (hr)	Treatment 5A	Treatment 5B	Treatment 5C	Treatment 5D
48	0.18	0.20	0.20	0.19
60	0.09	0.10	0.09	0.09
72	0.06	0.06	0.04	0.05

TABLE 27

Pharmacokinetic Parameters of Plasma
6-Hydroxyoxymorphone for Study 5

	Treatment 5A		Treatment 5B		Treatment 5C		Treatment 5D	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max}	1.88	0.69	1.59	0.63	6.41	3.61	3.79	1.49
T_{max}	1.48	1.18	2.73	1.27	0.73	0.47	1.18	0.74
$AUC_{(0-t)}$	28.22	10.81	26.95	11.39	33.75	10.29	32.63	13.32
$AUC_{(0-inf)}$	33.15	11.25	32.98	10.68	37.63	17.01	36.54	13.79
$T_{1/2el}$	17.08	7.45	21.92	8.41	16.01	6.68	16.21	7.42

The above description incorporates preferred embodiments and examples as a means of describing and enabling the invention to be practiced by one of skill in the art. It is imagined that changes can be made without departing from the spirit and scope of the invention described herein and defined in the appended claims.

We claim:

1. An oral controlled release oxymorphone formulation, comprising:

a. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone; and

b. a hydrophilic material,

wherein upon oral administration of the formulation to a subject in need of an analgesic effect:

(i) the formulation provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5;

(iv) the duration of the analgesic effect is through at least about 12 hours after administration; and

(v) the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

2. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

3. The formulation of claim 1 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

4. The formulation of claim 3 wherein the gum is selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

5. The formulation of claim 1 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

6. The formulation of claim 1 wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

7. The formulation of claim 1 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

8. The formulation of claim 7 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

9. The formulation of claim 7 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

10. The formulation of claim 7 wherein the cross-linking agent is a homopolysaccharide gum.

11. The formulation of claim 1 further comprising a hydrophobic polymer.

12. A method of treating pain in a subject in need thereof, the method comprising the step of administering to the subject the formulation of claim 1.

13. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and controlled release granules comprising a hydrophilic material and one or more optional excipients; and

b. directly compressing the mixture of (a) to form the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

14. The tablet preparation of claim 13 wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

15. The tablet preparation of claim 13 wherein the hydrophilic material is a gum selected from the group consisting of a heteropolysaccharide gum, a homopolysaccharide gum, and mixtures thereof.

16. The tablet preparation of claim 13 wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

17. The tablet preparation of claim 13 wherein the hydrophilic material is hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

18. The tablet preparation of claim 13 wherein the hydrophilic material comprises at least one of:

i. a heteropolysaccharide; or

ii. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

iii. a mixture of (i), (ii) and a polysaccharide gum.

19. The tablet preparation of claim 18 wherein the heteropolysaccharide is a water soluble polysaccharide containing two or more kinds of sugar units and having a branched or helical configuration.

20. The tablet preparation of claim 19 wherein the heteropolysaccharide is selected from the group consisting of xanthan gum, deacylated xanthan gum, carboxymethyl ether xanthan gum, propylene glycol ester xanthan gum and mixtures thereof.

21. A pharmaceutical tablet prepared by:

a. mixing oxymorphone or a pharmaceutically acceptable salt of oxymorphone and one or more controlled release excipients; and

b. forming the tablet,

wherein upon placement of the tablet in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and wherein upon oral administration to a human subject the tablet alleviates pain for 12 to 24 hours.

22. The tablet of claim 21 wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

23. The tablet of claim 21 wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

24. The tablet of claim 21, wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

25. The tablet of claim 21, wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

26. The tablet of claim 21, wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

27. The tablet of claim 21, wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

28. The tablet of claim 21, wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

29. The tablet of claim 21, wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

30. The tablet of claim 21, wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

31. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form of a controlled release oxymorphone formulation with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

32. The method of claim **31** wherein the dosage form comprises about 40 mg oxymorphone or a pharmaceutically acceptable salt thereof, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

33. The method of claim **31** wherein the dosage form comprises about 20 mg oxymorphone or a pharmaceutically acceptable salt thereof.

34. The method of claim **31** wherein the dosage form comprises about 20 mg to about 40 mg oxymorphone hydrochloride.

35. The method of claim **31** wherein the difference in the oxymorphone area under the curve ($AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

36. The method of claim **35** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

37. The method of claim **31** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

38. A method for treating pain in a human subject in need of acute or chronic pain relief, comprising the steps of:

(a) Providing a solid oral dosage form comprising about 5 mg to about 80 mg oxymorphone or a pharmaceutically acceptable salt thereof in a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period, wherein oxymorphone is the sole active ingredient, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test; and

(b) administering a single dose of the dosage form to the subject,

wherein the oxymorphone C_{max} is at least 50% higher when the dosage form is administered to the subject under fed versus fasted conditions.

39. The method of claim **38** wherein the oxymorphone C_{max} is at least about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

40. The method of claim **38** wherein the difference in the oxymorphone area under the curve $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is less than 20%.

41. The method of claim **40** wherein the difference in $AUC_{(0\text{-}inf)}$ between fed and fasted conditions is about 18%.

42. The method of claim **38** wherein upon oral administration of the dosage form to the subject under fed or fasting conditions:

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of $AUC_{(0\text{-}inf)}$ of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

43. The method of claim **38** wherein the system further comprises a hydrophilic material.

44. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of a gum, a cellulose ether, an acrylic resin, a protein-derived material, and mixtures thereof.

45. The method of claim **44** wherein the hydrophilic material is a gum selected from the group consisting of xanthan, tragacanth, acacia, karaya, alginates, agar, guar, hydroxypropyl guar, carrageenan, locust bean, and mixtures thereof.

46. The method of claim **43** wherein the hydrophilic material is a cellulose ether selected from the group consisting of a hydroxyalkyl cellulose, a carboxyalkyl cellulose, and mixtures thereof.

47. The method of claim **43** wherein the hydrophilic material is selected from the group consisting of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, and mixtures thereof.

48. The method of claim **43** wherein the hydrophilic material comprises at least one of:

a. a heteropolysaccharide; or

b. a heteropolysaccharide and a cross-linking agent capable of cross-linking the heteropolysaccharide; or

c. a mixture of (a), (b) and a polysaccharide gum.

49. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37°

C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

50. The composition of claim **49** wherein upon oral administration thereof the oxymorphone $AUC_{(0\text{-}inf)}$ is no more than 20% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

51. The composition of claim **49** wherein the dosage form comprises about 40 mg oxymorphone, and wherein the oxymorphone C_{max} is about 58% higher when the dosage form is administered to the subject under fed as compared to fasted conditions.

52. The composition of claim **49** wherein the controlled release delivery system comprises a heteropolysaccharide and an agent capable of cross-linking the heteropolysaccharide in presence of gastrointestinal fluid.

53. The composition of claim **52** wherein the heteropolysaccharide and the agent capable of cross-linking the heteropolysaccharide are present in a weight ratio of about 1:3 to about 3:1.

54. The composition of claim **49** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

55. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels of oxymorphone and 6-hydroxy-oxymorphone over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

56. The composition of claim **55**, wherein upon oral administration of a single dose of the composition to a human subject, the oxymorphone C_{max} is at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions.

57. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test, at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test, at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test, at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test, at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test, at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test, and at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

58. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 27%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test.

59. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 40%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 2 hours in the test.

60. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 3 hours in the test.

61. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 64%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 5 hours in the test.

62. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 70%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 6 hours in the test.

63. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 79%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 8 hours in the test.

64. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 85%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

65. The composition of claim **55**, wherein the composition is in the form of a tablet and wherein at least 89%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 12 hours in the test.

66. An analgesically effective controlled release pharmaceutical composition for oral delivery, comprising:

a. a controlled release delivery system with a release rate profile designed to provide adequate blood plasma levels over at least 12 hours to provide sustained pain relief over this same period; and

b. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt of oxymorphone, wherein oxymorphone is the sole active ingredient,

wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 1 hour in the test, and wherein upon oral administration of the composition to a human subject, the blood plasma levels of oxymorphone comprise one or more peaks.

67. The composition of claim **66** wherein the blood plasma levels comprise two peaks.

68. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect:

(i) the composition provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration; and

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5.

69. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an anal-

gesic effect the blood plasma levels of oxymorphone exhibit two or three peaks within about 12 hours after administration.

70. The composition of claim **66** wherein upon oral administration of the composition to a subject in need of an analgesic effect the blood plasma levels of oxymorphone comprise a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration.

71. The composition of claim **66** wherein the composition is in the form of a tablet and about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 4 hours in the test, and at least about 80%, by weight, of the oxymorphone or salt thereof is released from the tablet at about 10 hours in the test.

72. A controlled release pharmaceutical composition comprising oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient and a controlled release matrix, comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test.

73. The pharmaceutical composition of claim **72** wherein about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

74. The pharmaceutical composition of claim **72** wherein at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

75. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises one or peaks.

76. The pharmaceutical composition of claim **72** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect, the blood plasma concentration of oxymorphone comprises a first peak at about 3 hours after administration and a second peak at about 6-7 hours after administration; and wherein

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

77. A controlled release pharmaceutical composition comprising oxymorphone or pharmaceutically acceptable salt thereof as the sole active ingredient, and a controlled release matrix comprising about 10% to about 75% (by total weight of the controlled release matrix) of a gelling agent which forms a gel upon exposure to gastrointestinal fluid;

wherein upon placement of the composition in an in vitro dissolution test comprising USP paddle method at 50 rpm in 500 ml media having a pH of 1.2 to 6.8 at 37° C., about 15% to about 50%, by weight, of the oxymorphone or salt thereof is released from the composition after about 1 hour in the test, about 45% to about 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test, and at least 80%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test,

wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0\text{-}inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

78. The pharmaceutical composition of claim **77** wherein upon oral administration of the dosage form to a human subject in need of an analgesic effect the blood plasma level of oxymorphone displays two or three peaks over about the first 12 hours after administration; and

(i) the dosage form provides detectable blood plasma levels of 6-OH oxymorphone and oxymorphone;

(ii) the blood plasma levels of 6-OH oxymorphone and oxymorphone peak within about 1 hour to about 8 hours after administration;

(iii) the blood plasma levels of 6-OH oxymorphone and oxymorphone exhibit a ratio of area under the curve ($AUC_{(0\ to\ inf)}$) of blood plasma level versus time for 6-OH oxymorphone compared to oxymorphone in a range of about 0.5 to about 1.5; and

(iv) the duration of the analgesic effect is through at least about 12 hours after administration.

79. The pharmaceutical composition of claim **77** wherein about 58% to about 66%, by weight, of the oxymorphone or salt thereof is released from the composition after about 4 hours in the test.

80. The pharmaceutical composition of claim **77** wherein about 85% to about 96%, by weight, of the oxymorphone or salt thereof is released from the composition after about 10 hours in the test.

81. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **72** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof, wherein upon oral administration of a single dose of the composition to a human subject, the composition provides an oxymorphone C_{max} of at least 50% higher when the dose is administered to the subject under fed as compared to fasted conditions and provides a difference in oxymorphone $AUC_{(0\text{-}inf)}$ of less than 20% higher when the dose is administered to the subject under fed as compared to fasted conditions.

82. A method of treating pain in a subject in need thereof, the method comprising administering to the subject the pharmaceutical composition of claim **77** in an amount sufficient to provide the subject with about 5 mg to about 80 mg of oxymorphone or salt thereof.

* * * * *

EXHIBIT CC

KeyCite Yellow Flag - Negative Treatment
Distinguished by Silver Buckle Mines, Inc. v. United States, Fed.Cl., May 23, 2017

746 F.3d 1371
United States Court of Appeals,
Federal Circuit.

ENDO PHARMACEUTICALS INC., Plaintiff–Appellant,
v.
ACTAVIS, INC. and Actavis South Atlantic, LLC, Defendants–Appellees.
Endo Pharmaceuticals Inc., Plaintiff–Appellant,
v.
Roxane Laboratories, Inc., Defendant–Appellee.

Nos. 2013–1658, 2013–1662.
|
March 31, 2014.
|
Rehearing En Banc Denied June 3, 2014.

Synopsis

Background: Owner of patents directed to extended-release oxymorphone compositions and methods of treating pain using those compositions brought infringement action against manufacturers of generic drugs. Patentee moved for preliminary injunction to prohibit manufacturers from marketing and selling generic drug products during pendency of litigation. The United States District Court for the Southern District of New York, Thomas P. Griesa, Senior District Judge, denied motion. Patentee appealed.

Holdings: The Court of Appeals, Moore, Circuit Judge, held that:

[1] manufacturers did not have express license to practice asserted patents, and

[2] patent owner was not estopped from bringing infringement claims.

Vacated and remanded.

Dyk, Circuit Judge, filed an opinion dissenting in part.

West Headnotes (8)

[1] **Federal Courts**
Preliminary injunction;temporary restraining order

Court of Appeals reviews decisions to grant or deny a preliminary injunction for an abuse of discretion, which may be established when a district court based its decision on an error of law.

1 Cases that cite this headnote

[2] **Patents**
Assignor, grantor, or licensor

Patents
Implied license

Whether legal estoppel has been created and whether an implied patent license exists are questions of law.

1 Cases that cite this headnote

[3] **Patents**
License

The burden of proving that an implied license exists is on the party asserting an implied license as a defense to patent infringement.

4 Cases that cite this headnote

[4] **Patents**
Construction and Operation of Licenses

Asserted patents directed to extended-release oxymorphone compositions and methods of treating pain using those compositions were not continuations, continuations-in-part, or divisionals of previously licensed patents, and thus manufacturers of generic drugs did not have express license to practice any of the patents asserted in infringement action under license agreement for other patents. 35 U.S.C.A. § 120; 37 C.F.R. § 1.78(d)(2).

4 Cases that cite this headnote

[5] **Patents**
Assignor, grantor, or licensor

Owner of patents directed to extended-release oxymorphone compositions and methods of treating pain using those compositions was not estopped from bringing infringement claims against manufacturers of generic drugs, although manufacturers had licenses to use other patents held by patentee; none of the asserted patents were continuation of any of the licensed patents, and license agreement contained explicit disclaimer of any other licenses not within literal terms of license agreement. 35 U.S.C.A. § 154.

3 Cases that cite this headnote

[6] **Patents**
Assignor, grantor, or licensor

The doctrine of legal estoppel refers to a narrow category of conduct encompassing scenarios where a patentee has licensed or assigned a right, received consideration, and then sought to derogate from the right granted.

1 Cases that cite this headnote

[7] **Patents**
Construction and Operation of Licenses

Patent license agreements can be written to convey different scopes of promises not to sue, e.g., a promise not to sue under a specific patent or, more broadly, a promise not to sue under any patent the licensor now has or may acquire in the future.

Cases that cite this headnote

[8] **Patents**
In general;utility

US Patent 5,662,933, US Patent 5,958,456, US Patent 7,276,250, US Patent 7,851,482, US Patent 8,309,122, US Patent 8,329,216. Cited.

Cases that cite this headnote

Attorneys and Law Firms

***1372** Martin J. Black, Dechert LLP, of Philadelphia, PA, argued for plaintiff-appellant. With him on the brief were Robert D. Rhoad and Jonathan D. Loeb. Of counsel were Vincent August Gallo and Joseph Raymond Heffern.

Charles A. Weiss, Holland & Knight LLP, of New York, NY, argued for defendants-appellees, Actavis, Inc., et al. With him on the brief were Eric H. Yecies and Nicholas P. Chiara.

Alan B. Clement, Locke Lord LLP, of New York, NY, argued for defendant-appellee, Roxane Laboratories, Inc. With him on the brief were Keith D. Parr, Hugh S. Balsam, and Myoka Kim Goodin, of Chicago, IL.

Before NEWMAN, DYK, and MOORE, Circuit Judges.

Opinion

MOORE, Circuit Judge.

Endo Pharmaceuticals, Inc. (Endo) appeals from the district court's order denying its motions for a preliminary injunction to prevent Roxane Laboratories, Inc. (Roxane), Actavis Inc., and Actavis South Atlantic LLC (Actavis) from marketing and selling their respective generic drug products during the pendency of this litigation. Because the district court erred in concluding that Roxane and Actavis (Appellees) had an implied license to practice the asserted patents, and because Appellees do not have an express license, we *vacate* and *remand.*

BACKGROUND

Endo sells Opana® ER, which are branded extended-release tablets containing a painkiller called oxymorphone. The asserted patents are listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) entry for Opana® ER. Two of the asserted patents, U.S. Patent Nos. 8,309,122 (the #122 patent) and 8,329,216 (the #216 patent), are each

continuations of the same parent application and are directed to extended-release oxymorphone compositions and methods of treating pain using those compositions. The third patent-in-suit, U.S. Patent No. 7,851,482 (the #482 patent), is not related to the other two patents. It recites purified oxymorphone compositions and methods of making those compositions. The #122 and #216 patents are at issue in both appeals, and the #482 patent is at issue only in the Actavis appeal.

Prior to this litigation, Endo sued Appellees for patent infringement under 35 U.S.C. § 271(e)(2)(A) based on their Abbreviated New Drug Applications (ANDAs) to market generic versions of Opana® ER-the same products as those at issue in these appeals. The first set of ***1373** lawsuits settled after Endo granted to Appellees a license and a covenant not to sue. The settlement and license agreement between Endo and Roxane (Roxane Agreement) defines "Licensed Patents" as follows:

> (a) any [U.S.] patents that are *both* (i) *now owned* by Endo ... and (ii) *issued as of the Effective Date of this Agreement,* including the Opana® ER Patents,
>
> (b) *any [U.S.] patent applications that claim priority to the Opana® ER Patents, including any continuation,* continuation-in-part and divisional *patent applications that claim priority to Opana® ER Patents,* and
>
> (c) any patents resulting from the reissue or reexamination of patents or patent application of patents or patent applications comprised within clauses (a) and (b) ...

J.A. in appeal no. 2013–1662 (Roxane J.A.), at 4973 § 1.16 (emphases added). The Roxane Agreement defines "Opana® ER Patents" as U.S. Patent Nos. 5,662,933, 5,958,456, and 7,276,250. *Id.* § 1.20.

Pursuant to the agreement, Endo granted Roxane a covenant that it would not assert that Roxane's generic versions of Opana® ER "infringe[ ] the *Licensed Patents* " and a license "*under the Licensed Patents* ... to make, use, have made, sell, offer to sell, import and use" those generic products. Roxane J.A. 4978 §§ 4.1(a),(b) (emphases added); *see also* Roxane J.A. 4974 §§ 1.28, 1.29. Finally, the Roxane Agreement includes a "No Implied Rights" provision stating that Endo does not grant to Roxane any license or right "whether by implication, estoppel or otherwise, other than as expressly granted herein." Roxane J.A. 4949 § 4.4. The settlement and license agreement between Endo and Actavis (Actavis Agreement) is similar. The Actavis Agreement includes a grant of a license, a covenant not to sue, and a "No Implied Rights" provision, but covers one additional patent not included in the Roxane Agreement and not relevant to this appeal. J.A. in appeal no. 2013–1658 (Actavis J.A.), at 4893–908.

The patents that are the subject of this litigation issued after Endo's agreements with Appellees. The #122 and #216 patents issued to Endo and the #482 patent was acquired by Endo. Endo again sued Appellees for patent infringement under 35 U.S.C. § 271(e)(2)(A) and moved for a preliminary injunction to prevent the marketing and sales of their generic oxymorphone formulations. Appellees opposed on the theories of express license and implied license by reason of legal estoppel. With regard to the latter, Appellees argued that Endo attempted to deprive them "of the benefit of [the] earlier bargain." Roxane J.A. 4823; *see also* Actavis J.A. 2717.

At a joint hearing, the district court commented that "this is a highly unfair and unjust situation if ... infringement of the new patents would stop the marketing and permitting process that was going on by Actavis and Roxane." Actavis J.A. 6411. The court held that "as a matter of law ... Endo is estopped from claiming that the activity of Actavis and Roxane, which has gone on for a substantial period of time, is now suddenly barred because of these new patents." *Id.* The court therefore denied Endo's motions. *Endo Pharm., Inc. v. Actavis Inc.,* C.A. No. 12–cv–8985–TPG (S.D.N.Y. Sept. 18, 2013), ECF No. 35.

Endo appeals. We have jurisdiction under 28 U.S.C. § 1292(a)(1).

DISCUSSION

[1] **[2]** **[3]** We review decisions to grant or deny a preliminary injunction for an abuse of discretion, which may be established ***1374** when a district court based its decision on an error of law. *Sanofi–Synthelabo v. Apotex, Inc.,* 470 F.3d 1368, 1374 (Fed.Cir.2006). "To the extent the court's decision is based upon an issue of law, we review that issue *de novo.*" *Id.* Whether legal estoppel has been created and whether an implied license exists are questions of law. *Wang Labs., Inc. v. Mitsubishi Elecs.*

Am., Inc., 103 F.3d 1571, 1578, 1580 (Fed.Cir.1997). "The interpretation of a Settlement Agreement, *i.e.,* a contract, is a question of law that we [also] review *de novo.*" *Augustine Med., Inc. v. Progressive Dynamics, Inc.,* 194 F.3d 1367, 1370 (Fed.Cir.1999). "The burden of proving that an implied license exists is on the party asserting an implied license as a defense to infringement." *Id.*

I. Express License

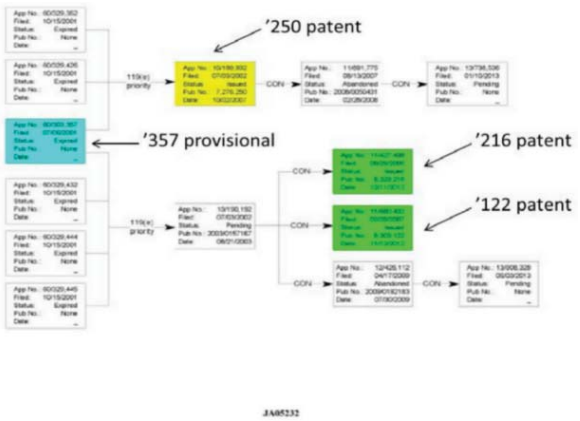
[4] Endo argues that the district court abused its discretion in denying Endo's motions for a preliminary injunction. Endo contends that the plain language of the agreements, which limit "Licensed Patents" to several enumerated patents and applications claiming priority to them, does not grant Appellees an express license to practice the asserted patents. It argues that the "No Implied Rights" provision further makes clear that the agreements do not cover the asserted patents. In the district court, both Actavis and Roxane argued that they have an express license to practice these newly issued patents. In this appeal, Actavis no longer presents this argument, although Roxane continues to do so. The district court did not decide the question of express license, stating that "I do not feel, for the purposes of a preliminary injunction motion, that I am able to make any findings on the issues that I have just described." Actavis J.A. 6438.

Roxane responds that the express terms of the settlement and license agreement grant it a license to practice the asserted patents because the previously licensed U.S. Patent No. 7,276,250 (#250 patent) claims priority to U.S. Provisional Application No. 60/303,357 (#357 application), and the #122 and #216 patents also claim priority to that provisional application. It contends that the word "including" in § 1.16(b) of the Roxane Agreement shows that the agreement covers more than just continuation, continuation-in-part, and divisional applications that claim priority to the Opana® ER Patents. Roxane argues that this section "necessarily embraces any patent applications that claim priority to any applications and provisional applications" to which the licensed patents likewise claim priority. Roxane Br. 29. It contends that Endo's interpretation reads out the word "including" and other license terms, and argues that the common provisional application teaches subject matter that "binds" the #250 patent to the asserted #122 and #216 patents.

Roxane's express license arguments are meritless. Section 1.16(b) of the Roxane Agreement covers U.S. patent applications that "claim priority to the Opana® ER Patents [*e.g.,* any of the licensed patents], including any continuation, continuation-in-part and divisional patent applications that claim priority to Opana® ER Patents." Roxane J.A. 4973 § 1.16(b). There can be no dispute that the #122 and #216 patents are not continuations of any of the licensed patents.[1] Likewise, there is no reasonable ***1375** argument that the #122 and #216 patents claim priority to any of the licensed patents. An application that claims priority to another patent must contain an express cross-reference to "a prior-filed nonprovisional application from which the patent issued." 37 C.F.R. § 1.78(d)(2) (2013); *see* 35 U.S.C. § 120 (2012); *Encyclopaedia Britannica, Inc. v. Alpine Elecs. of Am., Inc.,* 609 F.3d 1345, 1351 (Fed.Cir.2010). The #216 and #122 patents, however, do not cross-reference the applications that issued as any of the licensed patents. *See* #122 patent col. 1 ll. 6–7; #216 patent col. 1 ll. 6–7. Therefore, it is quite clear that the #122 and #216 patents do not "claim priority to" any of the licensed patents.

1 We note that counsel for Actavis repeatedly argued to the district court that the #122 and #216 patents are continuations of the # 250 patent and are therefore expressly licensed. *See, e.g.,* Actavis J.A. 2716 ("Endo's #122 patent and #216 patent are continuations of a patent called out by number as licensed in the 2009 settlement and license agreement."). This is flatly wrong, and it is difficult to believe that this argument was made given what is required for an application to be a continuation. For example, to be called a "continuation" of a prior patent, a patent must make an express cross-reference to the nonprovisional application from which the prior patent issued. The continuation must also have the same disclosure as the prior patent. *See* Manual of Patent Examining Procedure (MPEP) § 201.07 (8th ed. Rev.9, Oct. 2012). The # 122 and #216 patents do not have the same disclosure as the #250 patent, nor do they claim priority to the application that issued as the # 250 patent. To be continuations of the #250 patent, the #122 and # 216 patents would have to, on their face, expressly indicate that they are continuations of the application that issued as the #250 patent—unequivocally, they do not.

Roxane's argument that the word "including" somehow broadens what it means "to claim priority to" another patent is unpersuasive. The Roxane Agreement covers "any applications that claim priority to the [#250 patent], including any continuation, continuation-in-part and divisional" patent applications. Roxane J.A. 4973. Claiming priority to a licensed patent is a prerequisite for the license, and "including" by no means eviscerates that requirement. There is no reading of this language that extends coverage to patents that merely have a provisional application in common with the licensed patents. The figure reproduced below, which is part of the record, shows this clearly. *See* Roxane J.A. 5232. The #122 and #216 patents claim priority to the #357 provisional application, and the #250 patent claims priority to the #357 application as well. The #122 and #216 patents *do not* claim priority to the #250 patent. Although the language is clear on its face, the fact that Endo and Roxane considered including in their agreement a grant of a license to "any application *claiming a common priority date as* the licensed patents" reinforces this conclusion. Roxane J.A. 4864–65 (emphasis added). Because the #122 and # 216 patents have a provisional application in common with the #250 patent, the "common priority date" language would have expressly covered the # 122 and #216 patents. *See* 35 U.S.C. § 119(e)(1) (2012). But that language does not appear in the final version of the Roxane Agreement.



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***1376** The Actavis Agreement likewise does not cover the #122, #216, and #482 patents at issue in the Actavis appeal. It contains the same "continuations, continuations-in-part or divisionals" language as the Roxane Agreement. *See* Actavis J.A. 4893, 4895, 4898. For the reasons discussed above, the asserted patents are not continuations, continuations-in-part, or divisionals of the licensed patents. *See* MPEP §§ 201.06–.08. Finally, the #482 patent is completely unrelated to any of the previously licensed patents, and is likewise not covered by the agreement. We hold that Appellees do not have an express license to practice any of the patents asserted in this litigation.

II. Implied License

[5] Endo argues that the district court legally erred in concluding that Appellees are impliedly licensed to practice the asserted patents due to legal estoppel. It contends that the court's recognition of an implied license defense is incorrect. It argues that the specifications of the asserted patents are different from those of the previously licensed patents, and that the claims cover different subject matter. Endo points out that the previously licensed patent (the #250 patent) that claims priority to the same provisional application as the #122 and #216 patents was not even asserted in the previous litigation, and only added to the final settlement and license agreements because Endo realized that Appellees did not infringe it. Endo argues that, in contrast, the #122 and #216 patents—and the unrelated # 482 patent—cover the accused generic tablets. Endo argues that the cases relied upon by Appellees regarding estoppel are distinguishable because they involved continuations and because the licenses in those cases included products as well as patents. Endo argues that, by ignoring the language of the agreements and the parties' intent, the district court's approach violates the sanctity of contract and thus implicates serious public policy concerns.

Appellees respond that they have an implied license to practice the asserted patents based on the principle that equity does not permit the licensor to detract from its grant of a property right. Appellees contend that Endo granted them a license to market their accused generic ***1377** products for valuable consideration, that they relied on the license in going forward with the Food and Drug Administration approval of the ANDAs, and that Endo's later-obtained patents "eviscerated" the benefit of the licenses. Appellees argue that the "No Implied Rights" language in the agreements is not dispositive because estoppel "must override any such provision." Roxane Br. 22; *see* Actavis Br. 29–30.

Appellees contend that the facts here are analogous to those in *TransCore, LP v. Electronic Transaction Consultants Corp.,* where we held that the patentee was

legally estopped from bringing a second infringement action even though the earlier settlement agreement stated that it "shall not apply to any other patents." 563 F.3d 1271, 1279 (Fed.Cir.2009). They argue that *TransCore* and related cases dictate that Endo cannot deprive Appellees of the benefit of the earlier bargain, and that nothing in the reasoning of *TransCore* limits its holding to continuations or even related applications. Appellees contend that the settlement and license agreements should be deemed as allowing them to make, use, and sell their generic tablets without threat of further lawsuits by Endo.

We hold that Appellees' broad reading of *TransCore* is incorrect and agree with Endo that the district court erred as a matter of law in finding legal estoppel in favor of Actavis and Roxane. We begin with the well-established proposition, recognized in *TransCore,* that a patent license does not convey to the licensee "an absolute right" to make, use, or sell a product "because not even the patentee ... is given that right." *Spindelfabrik Suessen–Schurr, Stahlecker & Grill GmbH v. Schubert & Salzer Maschinenfabrik Aktiengesellschaft,* 829 F.2d 1075, 1081 (Fed.Cir.1987) (quoted in *TransCore,* 563 F.3d at 1275–76). The patentee's right "is merely one to exclude others from making, using or selling [the product covered by the licensed patent], 35 U.S.C. § 154" and "the patentee ... and his licensee, when making, using, or selling [the product], can be subject to suit under other patents" when practicing the patented invention. *Id.*

[6] The doctrine of legal estoppel does not nullify these general principles. Instead, it "refers to a *narrow category of conduct* encompassing scenarios where a patentee has licensed or assigned a right, received consideration, and then sought to derogate from the right granted." *TransCore,* 563 F.3d at 1279 (alteration omitted) (emphasis added). In *TransCore,* the patentee asserted a continuation patent that "was broader than, and necessary to practice" one of the patents included in a prior settlement agreement. *Id.* We observed that the fact that the patentee "adopted its [licensed] patent infringement contentions as its contentions related to the [asserted] patent," *id.,* provided undisputed evidence that the patentee "sought to enforce the [asserted] patent in derogation of the rights it granted" under the prior agreement, *id.* at 1279 n. 4. Even though the agreement stated that it "shall not apply to other patents ... to be issued in the future," we concluded that the patentee was legally estopped from asserting a patent whose claim scope fully encompassed that of the claims of one of the licensed patents. *Id.* at 1279. We thus recognized that the asserted patent claims were broader than the licensed claims. To avoid a windfall to the licensee, we expressly limited the implied license to the scope of the licensed claims. *Id.* ("[T]o obtain the benefit of its bargain with [the licensor], [the licensee] must be permitted to practice the [asserted patent] to the same extent it may practice the [licensed patents]."); *id.* at 1279–80 ("[Licensee's] rights under its implied license to the [asserted patent] are necessarily ***1378** coextensive with the rights it received in the ... license agreement.").

Our subsequent cases confirm the limited scope of *TransCore.* In *General Protecht Group, Inc. v. Leviton Manufacturing Co., Inc.,* we found an implied license where the asserted patents had "[t]he same inventive subject matter [as that] disclosed in the licensed patents" and "[t]he same products were accused." 651 F.3d 1355, 1361 (Fed.Cir.2011). As in *TransCore,* the patents at issue in *General Protecht* were *continuations* of the licensed patents. *See id.* at 1360 (quoting *TransCore,* 563 F.3d at 1279–80). We observed that "the newly asserted continuations are based on the same disclosure as the previously licensed patents and that, by definition, the continuations can claim no new inventions not already supported in the earlier issued patents." *Id.* at 1361. After explaining that *TransCore* "prohibits a patent licensor from derogating from rights granted under the license," we held that "where ... *continuations issue from parent patents that previously have been licensed as to certain products,* it may be presumed that, absent a clear indication of mutual intent to the contrary, those products are impliedly licensed under the continuations as well." *Id.* (emphasis added). In *Intel Corp. v. Negotiated Data Solutions, Inc.,* we explained that *TransCore* and *General Protecht* "analyzed a licensee's rights when the patent holder received a *continuation patent* " and "recognized that allowing the patent holder to sue on subsequent patents, when those later patents contain *the same inventive subject matter that was licensed,* risks derogating rights for which the licensee paid consideration." 703 F.3d 1360, 1366 (Fed.Cir.2012) (emphases added). Taken together, these cases stand for the rule that a license or a covenant not to sue enumerating specific patents may legally estop the patentee from asserting *continuations* of the licensed patents in the absence of mutual intent to the contrary. *See Gen. Protecht,* 651 F.3d at 1361; *TransCore,* 563 F.3d at 1279. We reject Appellees' invitation to expand

the implied license doctrine. You get what you bargain for. And we will not use the implied license doctrine to insert ourselves into that bargain and rewrite the contract.

Endo is not estopped from asserting the patents at issue in these appeals because none of the asserted patents is a continuation of any of the licensed patents. The only familial relationship between the asserted and licensed patents is that the #122 and #216 patents claim priority to the same provisional application as the #250 patent. That, however, does not make these patents continuations of the #250 patent. *See* MPEP § 201.07. The #482 patent is not related to any of the licensed patents. The lack of a continuation relationship between any of the asserted and licensed patents and explicit disclaimer of any other licenses not within the literal terms of the contract are dispositive.

Appellees rely heavily on the general rule that "[t]he grantor is estopped from taking back in any extent that for which he has already received consideration." Actavis Br. 27 (quoting *TransCore,* 563 F.3d at 1279 (quoting *AMP Inc. v. United States,* 389 F.2d 448, 452 (Ct.Cl.1968))); *see also* Roxane Br. 20–21. But this rule does not apply to the cases before us because, unlike accused infringers in *TransCore* and *General Protecht,* Appellees seek to capture via implied license subject matter *in addition to that* for which they bargained. *AMP* is not to the contrary because the agreement at issue in that case gave the Government the license "to practice, and cause to be practiced ... throughout the world, each *Subject Invention* "—rather than any specific patents. 389 F.2d at 450, 454 (emphasis added). *AMP* made clear ***1379** that "[t]he facet of this licensing agreement which is of crucial importance ... is that it licenses the Government to use an *idea* and not just the Byrem Patent itself." *Id.* at 454 (emphasis in original). By asserting a newly acquired patent covering the licensed invention, AMP derogated from its grant, and the Court of Claims concluded that AMP's patent infringement suit was barred by legal estoppel "in order to protect the specific rights granted to the Government by contract." *Id.* at 454.

[7] Here, rather than grant a license to an "idea," Endo has granted to Appellees a license and covenant not to sue limited to specific patents and patent applications. If Appellees wanted to market and sell their accused generic products free from any threat of being sued by Endo for patent infringement, they could have negotiated for the appropriate language in the settlement and license agreements. As we observed in *Spindelfabrik,* "patent license agreements can be written to convey different scopes of promises not to sue, *e.g.,* a promise not to sue under a specific patent or, more broadly, a promise not to sue under any patent the licensor now has or may acquire in the future." 829 F.2d at 1081 (quoted in *TransCore,* 563 F.3d at 1276). Having agreed to licenses that do not cover the patents at issue in these appeals, Appellees will not now be heard to complain.

CONCLUSION

We have considered the parties' remaining arguments and do not find them to be persuasive. We *vacate* the district court's denials of a preliminary injunction in both cases and *remand* for further proceedings.

VACATED AND REMANDED

Opinion dissenting in part filed by Circuit Judge DYK.

DYK, Circuit Judge, dissenting in part.

I agree with the majority that Roxane did not have an express or implied license to practice the #122 and #216 patents. Roxane was aware of Endo's applications for those patents at the time of the settlement with Endo, and the parties agreed not to include them in the settlement agreement. This, it seems to me, is inconsistent with an implied license. I also agree that Actavis does not have an implied license to the #482 patent, which Endo did not own at the time of the Actavis settlement agreement.

I part company with the majority on the question of whether Actavis has an implied license to the #122 and #216 patents. At the time of their settlement agreement, Endo owned those patent applications, which claimed priority to the same provisional application that provided priority to a patent covered by the settlement agreement (the #250 patent). During the settlement negotiations, Endo did not disclose the #122 and #216 patent applications, but rather licensed Actavis to produce the product at issue here. Furthermore, there are material differences between the Actavis and Roxane agreements and negotiations. Under these circumstances, I conclude that Actavis has an implied license to practice the #122

and #216 patents with respect to the product covered by the ANDA that was the subject of the settlement agreement. I respectfully dissent from the majority's contrary conclusion.

I

Under the Hatch–Waxman Act, pharmaceutical manufacturers filing a New Drug Application (NDA) must list patents in the FDA's Orange Book that "could reasonably be asserted" against a competing generic producer. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.53(c)(2)(ii). ***1380** Endo filed an NDA for a pain relief medication called Opana® ER on June 22, 2006 (NDA No. 21–610). Endo listed four patents covering the NDA product—the #250, #933, #456, and # 143 patents—in the Orange Book. The FDA approved Endo's NDA.

On February 14, 2008, Actavis sent Endo notice that it had filed an Abbreviated New Drug Application (ANDA) seeking FDA approval to market a generic version of Opana® ER, as did Roxane on December 21, 2009. After receiving these notices, Endo sued Actavis and Roxane (which had also filed a similar ANDA) in the United States District Court for the District of New Jersey, claiming that Actavis and Roxane's ANDA filings constituted an act of infringement. *See* 35 U.S.C. § 271(e)(2)(A). Endo asserted only the #456 patent in the complaint.

Before the litigation could proceed to trial, Endo entered into separate settlement and license agreements with Actavis in 2009 and Roxane in 2011, permitting these companies to sell generic versions of Opana® ER pursuant to their ANDA filings. Sections 4.1(a) and (b) of Actavis's agreement with Endo granted Actavis a license to produce and sell generic versions of Opana® ER under the #456 patent and specified that "Endo ... covenant[s] not to sue [*i.e.,* licenses] Actavis ... for infringement of ... the Opana® ER Patents [*i.e.,* the #250, #933, and #143 patents] based on the manufacture, use, import, sale or offer for sale of any Opana® ER Generic Products...." Actavis J.A. 3305. The Actavis agreement defined "Opana® ER Generic Product" as "any product that is ... sold under the Actavis ANDA." Actavis J.A. 3302. Sections 4.1(a) and (b) of Roxane's settlement agreement with Endo were similar.[1] Both agreements also contained clauses stating: "Endo ... do[es] not grant to Actavis [or Roxane] ... any license, right or immunity, whether by implication, estoppel or otherwise, other than as expressly granted herein." Actavis J.A. 3306; Roxane J.A. 4569. However, as I later discuss, Roxane's negotiation history and resulting agreement differed significantly in other respects from that of Actavis.

1 The Roxane agreement defined "Opana® ER Patents" as only the # 250, #456, and #933 patents because the #143 patent expired in 2008.

The FDA approved both Actavis's and Roxane's ANDAs, and those companies have been selling generic versions of Opana® ER under their ANDAs since 2011.

At the time of the settlement agreements, Endo had pending patent applications for the #122 and #216 patents. This was disclosed to Roxane but not to Actavis. After Actavis and Roxane began to sell their generic versions of Opana® ER pursuant to their settlement agreements, the PTO issued the #122 and #216 patents to Endo in November and December 2012, respectively. These patents cover Opana® ER's active ingredient as well as its slow release method. *See* U.S. Patent No. 8,309,122; U.S. Patent No. 8,329,216. Endo has now listed these new patents in the Orange Book as related to Opana® ER. The #122 and #216 patents claim priority to the same 2001 provisional application that gave priority to the #250 patent licensed under the settlement agreements.

In this case, Endo has sought to enjoin Actavis and Roxane's production of Opana® ER generic products on the ground that such sales infringe the #122 and #216 patents. Thus, the question is whether, as the district court held, these companies have implied licenses to produce the disputed products under their settlement agreements with Endo.

II

In my view, the majority's holding that Actavis has no right to an implied license ***1381** is inconsistent with our prior decisions in *TransCore, LP v. Electronic Transaction Consultants Corp.,* 563 F.3d 1271 (Fed.Cir.2009) and *General Protecht Group, Inc. v. Leviton Manufacturing Co., Inc.,* 651 F.3d 1355 (Fed.Cir.2011). The majority reads these cases as standing for the proposition "that a license or a covenant not to sue enumerating specific patents may legally estop the patentee from asserting *continuations* of the licensed patents in the absence of

mutual intent to the contrary." Majority Op. at 1378. I think there is no meaningful distinction between the provisional patent relationship at issue in this appeal and the continuation patent relationships at issue in our earlier decisions.

The logic driving *TransCore* and *General Protecht* is rooted in a decision of our predecessor court, *AMP Inc. v. United States,* 389 F.2d 448 (Ct.Cl.1968). Our predecessor court's decision in *AMP* recognized that a patentee may convey rights to future patents on that invention in licensing agreements even when the licensing agreement does not explicitly cover future patents on the same invention. *Id.* at 454–56. *TransCore* applied *AMP's* holding to a situation similar to the present appeals. *TransCore* held that a patentee cannot license existing patents to another party for the production of a specific product and then assert a newly acquired patent against that party to prevent it from producing the same product. *TransCore,* 563 F.3d at 1278–79. As the majority accurately summarizes, the patentee in *TransCore,* after agreeing to license the product under existing patents, "asserted a continuation patent that 'was ... necessary to practice' one of the patents included in a prior settlement agreement." Majority Op. at 1377 (quoting *TransCore,* 563 F.3d at 1279). Although the *TransCore* settlement agreement, similar to the settlement agreements at issue here, provided that " '[t]his Covenant Not To Sue shall not apply to any other patents ... to be issued in the future,' " 563 F.3d at 1273, we held that "in order for [the licensee] to obtain the benefit of its bargain with TransCore, it must be permitted to practice the [new patent] to the same extent it may practice the [licensed] patents." *Id.* at 1279. We further explained that "[t]his language may protect TransCore against broad claims that future patents generally are impliedly licensed, but it does not permit TransCore to derogate from the rights it has expressly granted and thus does not preclude a finding of estoppel." *Id.* Thus, *TransCore* clarified that an explicit disclaimer of any other license not within the literal terms of the contract does not protect the patentee from an implied license when such a license is necessary to ensure the licensee obtains "the benefit of its bargain." *Id.*

Similarly, in *General Protecht,* the patentee sued General Protecht for infringement of two patents, reached a license and settlement agreement with General Protecht allowing it to produce a defined product under the existing patents, and then, three years later, sued General Protecht again, alleging infringement of two new patents that issued after the settlement agreement. *Gen. Protecht,* 651 F.3d at 1357–58. The patentee argued that *TransCore* "d[id] not control" its appeal because *TransCore* "is limited to cases where the claims of the continuation are broader than and therefore necessary to practice the claims of the expressly licensed patents." *Id.* at 1361. In response, this court reasoned that

> [the patentee] cannot deny ... that the newly asserted continuations are based on the same disclosure as the previously licensed patents and that, by definition, the continuations can claim no new invention not already supported in the earlier issued patents. Moreover, the ***1382** same products accused in the earlier suit are accused here. *TransCore* prohibits a patent licensor from derogating from rights granted under the license by taking back in any extent that for which it has already received consideration. In this case, [the patentee's] actions have unquestionably derogated from [General Protecht]' s rights under the Settlement Agreement. *The same products were accused. The same inventive subject matter was disclosed in the licensed patents. If [the patentee] did not intend its license of these products to extend to claims presented in continuation patents, it had an obligation to make that clear.*

Id. (emphasis added) (internal quotation marks and citation omitted) (alteration in original omitted).

Here too, if Endo succeeds on its infringement allegations, Actavis will not be able to sell the very product for which it secured licenses in its settlement agreement. Although the #122 and #216 patents are not continuations of the licensed patents, as was the case in *TransCore* and *General Protecht,* the logic of those cases applies equally here. Under 35 U.S.C. § 119(e)(1), a patent that claims priority to a provisional application must "have the same effect, as to such invention [the provisional invention], as though filed on the date of the provisional application." 35 U.S.C.

§ 119(e)(1). Thus, as we have explained in the past, " '[w]hat is claimed by the patent application [claiming priority to a provisional application] must be the same as what is disclosed in the [provisional] specification.' " *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.,* 298 F.3d 1290, 1296 (Fed.Cir.2002) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.,* 535 U.S. 722, 122 S.Ct. 1831, 152 L.Ed.2d 944 (2002)) (citing *Lockwood v. Am. Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed.Cir.1997)); *see also Ariad Pharms. Inc. v. Eli Lilly & Co.,* 598 F.3d 1336, 1342 (Fed.Cir.2010). That is to say, a patent claiming priority to a provisional application must cover the same inventive subject matter as the provisional application.

Since the #250 patent (covered by the license agreements) and the # 122 and #216 patent applications (subsequently issued) claim priority to the same provisional application and, thus, must cover the same inventive subject matter, the agreements confer an implied license to the two new patents absent contrary evidence. In other words, under our decisions in *TransCore* and *General Protecht,* the settlement agreements here created a presumption that the #122 and #216 patents were impliedly licensed to Actavis and Roxane, even though the only licenses explicitly mentioned in the settlement agreements were to the #250, #456, and #933 patents.

III

Nevertheless, I also think that the parties can agree to eliminate the presumption of implied licenses. Under our prior decisions, this cannot be accomplished simply by stating that the agreement does not extend to any patents beyond those listed in the agreement. *TransCore* and *General Protecht* rejected this very contention. *See Gen. Protecht,* 651 F.3d at 1362–63; *TransCore,* 563 F.3d at 1279. Here, as to Roxane there is more. In the course of its negotiations with Endo, Roxane became aware of the #122 and #216 patent applications, sought to have these pending patents included in the agreement, and ultimately failed to secure a license to them. That history, it seems to me, is sufficient to negate an implied license. But the Actavis negotiations were different, having occurred two years before the Roxane agreement. The record contains no indication that the #122 and #216 patent applications ***1383** were discussed during Actavis–Endo negotiations or that Actavis was even aware of Endo's applications for the #122 and #216 patents.

While the majority states that the language of the Actavis and Roxane agreements is "similar," Majority Op. at 1373, there are, in fact, important differences. *Compare* Actavis J.A. 3300, 3302, 3305 *with* Roxane J.A. 4563, 4568. While both agreements provide an explicit license to produce generic versions of Opana® ER covered by Actavis's and Roxane's ANDAs under the # 250, #456, and #933 patents, clause (c) of the agreements is different. Clause (c) of the Actavis agreement reads:

> (c) For avoidance of doubt, and notwithstanding anything to the contrary in this Agreement, the License and Covenant Not to Sue do not grant to Actavis any rights or immunities with respect to any products *other than the Opana® ER Generic Products,* including any combination products.

Actavis J.A. 3305 (emphasis added). Critically, the agreement defines "Opana® ER Generic Products" as "*any product* that is marketed and/or sold under *the Actavis ANDA.*" Actavis J.A. 3302 (emphases added). Actavis sells the allegedly infringing product under the Actavis ANDA.

In contrast, clause (c) of the Roxane license agreement reads:

> (c) ... the License and Covenant Not to Sue does not grant to Roxane any rights or immunities with respect to any products other than the Roxane Products or *with respect to any patents other than the Licensed Patents.*

Roxane J.A. 4568 (emphasis added). The agreement defines "Licensed Patents" as

> (a) any United States patents that are both (i) *now owned* by Endo ... and (ii) *issued as of the Effective Date of this Agreement,* including the Opana® ER Patents, (b) any United States patent applications that *claim priority to the Opana® ER*

> *Patents,* including any continuation, continuation-in-part and divisional patent applications that claim priority to the Opana® ER Patents, and (c) any patents resulting from the reissue or reexamination of patents or parent applications comprised within clauses (a) and (b) above, in each case that Endo ... could assert would be infringing by the making, using, selling, offering to sell or importing of the Roxane Product.

Roxane J.A. 4563 (emphases added). Thus, while the Actavis license is only limited to "*any product* that is marketed and/or sold under the Actavis ANDA," Actavis J.A. 3302 (emphasis added), the Roxane license specifies that it neither extends to any other "products" *nor* "to any patents *other than the Licensed Patents,*" Roxane J.A. 4568 (emphasis added), *i.e.,* the 250, #456, and #933 patents. Thus, in subsection (c), the Actavis agreement does not limit the license to specific patents as the Roxane agreement does. A comparison of the two license agreements and the different negotiation histories suggests that Actavis could reasonably conclude it had negotiated a right to sell all Opana® ER generic products despite the interim issuance of the #122 and #216 patents, not merely practice the patents expressly licensed. [2]

2 With respect to the #482 patent, that patent does not claim priority to the provisional application, and the negotiating history does not suggest that Actavis could reasonably conclude that it had negotiated a license to all future patents that might be acquired by Endo relating to Opana® ER. Because the #482 patent issued to another company, Johnson Matthey, in 2010, was acquired by Endo in 2012, and does not claim priority to the provisional application, Actavis should not be treated as having an implied license to the #482 patent. Neither Endo nor Actavis could have known that Endo might later acquire this patent.

***1384** The majority concludes: "If Appellees wanted to market and sell their accused generic products free from any threat of being sued by Endo for patent infringement, they could have negotiated for the appropriate language in the settlement and license agreements." Majority Op. at 1379. But under that theory, this court's precedent in *TransCore* and *General Protecht* would have been wrongly decided. An implied license is not foreclosed simply because the parties could have negotiated for an express license. Here, as in *General Protecht,* Actavis's agreement allowed it to produce and sell a defined product, and we should imply licenses to the new patents because "the same products accused in the earlier suit are accused here," *Gen. Protecht,* 651 F.3d at 1361, and the patents relate to the same inventive subject matter claimed in the provision application.

That the #122 and #216 patent applications were published at the time of the settlement negotiations should not affect this conclusion: in both *General Protecht* and *TransCore,* at least one of the new patents at issue was published as a pending application at the time of the settlement and licensing negotiations. *See Gen. Protecht,* 651 F.3d at 1357–58 (the patentee and General Protecht entered into a licensing agreement in 2007, and then the patentee sued General Protecht for infringement of two new patents—U.S. Patent Nos. 7,463,124 and 7,764,151—in 2010); U.S. Patent No. 7,463,124 (first published on March 24, 2005, and issued on December 9, 2008); *TransCore,* 563 F.3d at 1273–74.

There is nothing unfair in granting an implied license in Actavis's favor. Although Actavis could have researched pending patent applications at the time of the settlement, placing the burden of disclosure on the party with greater access to information (here, Endo) increases the efficiency of the bargaining process. *See generally* Bruce L. Hay, *Effort, Information, Settlement, Trial,* 24 J. Legal Stud. 29, 31, 55–56, 62 (1995); Lucian Arye Bebchuk, *Suing Solely To Extract a Settlement Offer,* 17 J. Legal Stud. 437, 448 (1988); Lucian Arye Bebchuk, *Litigation and Settlement Under Imperfect Information,* 15 RAND J. Econ. 404, 414 (1984). Assigning this burden to the party with inferior access to information creates an incentive for the more knowledgeable party to hide information: the more informed party will not face repercussions for failing to disclose information, and, indeed, will benefit from such information asymmetries. *See generally* Bebchuk, *Suing Solely, supra,* at 448; Bebchuk, *Litigation and Settlement, supra,* at 414 ("[L]egal rules and institutions that magnify the extent to which an informational asymmetry is present might well increase the likelihood of litigation."); Richard A. Posner, *An Economic Approach to Legal Procedure and Judicial Administration,* 2 J. Legal Stud. 339, 422–26 (1973). By creating incentives to hide and obscure important information in settlement negotiations, we

undermine the purpose of the settlement process: the avoidance of further litigation.

I respectfully dissent.

All Citations

746 F.3d 1371, 110 U.S.P.Q.2d 1199

EXHIBIT DD

REDACTED IN ENTIRETY

EXHIBIT EE

UNITED STATES OF AMERICA
FEDERAL TRADE COMMISSION
OFFICE OF ADMINISTRATIVE LAW JUDGES

In the Matter of **Impax Laboratories, Inc.,** **a corporation,** **Respondent.**	**Docket No. 9373**

COMPLAINT COUNSEL'S OBJECTIONS AND RESPONSES TO RESPONDENT IMPAX LABORATORIES, INC.'S FIRST SET OF INTERROGATORIES TO COMPLAINT COUNSEL

Pursuant to Rules §§ 3.31 and 3.35 of the Federal Trade Commission's Rules of Practice for Adjudicative Proceedings, Complaint Counsel objects and responds to Respondent Impax Laboratories, Inc.'s First Set of Interrogatories to Complaint Counsel, dated May 30, 2017, as follows:

General Reservations and Objections

The following General Reservations and Objections apply to each Interrogatory and are incorporated by reference into each response made herein. The assertion of the same, similar, or additional objections, or providing partial answers in response to an individual Interrogatory does not waive any of Complaint Counsel's General Objections as to other Interrogatories.

1. Complaint Counsel objects to the Interrogatories, Definitions, and Instructions to the extent that they impose duties and obligations broader than those required or authorized by the Rules or any applicable order or rule of this Court.

2. Complaint Counsel objects to the Interrogatories, Definitions, and Instructions to the extent that they request information protected from disclosure by the work product doctrine, attorney-client privilege, or any other applicable privilege or doctrine.

3. Complaint Counsel objects to Interrogatories, Definitions, and Instructions to the extent that they seek information not reasonably expected to yield information relevant to the allegations in the Complaint, the proposed relief, or the defenses of Respondent.

4. Complaint Counsel objects to the Interrogatories, Definitions, and Instructions to the extent that they seek information that is not in its possession, custody, or control. Complaint Counsel further objects to the Interrogatories to the extent they seek information already in the possession of or easily obtainable by Impax.

5. Complaint Counsel objects to the Interrogatories, Definitions, and Instructions to the extent that they are vague, overly broad, and unduly burdensome.

6. Asserting the same, similar, or additional objections or providing partial answers in response to an individual Interrogatory does not waive any of Complaint Counsel's General or Specific Objections as to that Interrogatory or any other Interrogatories.

7. Neither these General Reservations and Objections, nor the Specific Objections and Responses set forth below are an admission regarding the relevance or admissibility of any response, or the truth or accuracy of any statement or characterization contained in any particular Interrogatory.

8. Unless otherwise indicated, Complaint Counsel will not provide information covered by the General Objections or the Specific Objections.

9. Discovery is ongoing in this action. Complaint Counsel's investigation and development of all facts and circumstances relating to this action is ongoing. The Responses set forth herein are based on Complaint Counsel's current knowledge, information, and belief. These Responses are subject to such additional or different information that discovery or further

investigation may disclose. Complaint Counsel reserves its right to supplement or amend its Responses as appropriate and to the extent required under Rule § 3.31(e).

Specific Objections and Responses

Based on and without waiving the General Reservations and Objections, or any other objections or claims of privilege, Complaint Counsel responds and objects to the Interrogatories as follows:

Interrogatory No. 1: If You contend that Endo made any payment or payments to Impax that were "large" and/or "unjustified," whether individually or collectively, state with specificity the factual basis for Your contention, including without limitation **(i)** the identity and value to Impax of each such payment; **(ii)** the identity and value to Endo of each such payment; **(iii)** why each such payment, or such payments collectively, were "large"; and **(iv)** why each such payment, or such payments collectively, were "unjustified."

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. There is no obligation to quantify with precision the value of the payment. Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 2: As of June 8, 2010, state with specificity the value of the Co-Exclusive License Provision **(i)** to Impax, and **(ii)** to Endo, including without limitation Your methodology for calculating these values; and identify with specificity all facts, Documents, Communications, data, reports, analyses, or other sources or materials upon which You based Your calculations.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. There is no obligation to quantify with precision the value of the payment. Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 3: As of June 8, 2010, state with specificity the value of the Endo Credit Provision **(i)** to Impax, and **(ii)** to Endo, including without limitation Your methodology for calculating these values; and identify with specificity all facts, Documents, Communications, data, reports, analyses, or other sources or materials upon which You based Your calculations.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. There is no obligation to quantify with precision the value of the payment. Instead, the question is whether the payment is

larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 4: As of June 8, 2010, state with specificity the value of the DCA **(i)** to Impax, and **(ii)** to Endo, including without limitation Your methodology for calculating these values; and identify with specificity all facts, Documents, Communications, data, reports, analyses, or other sources or materials upon which You based Your calculations.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. There is no obligation to quantify with precision the value of the payment. Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 5: If You contend that any payments made, owed, or potentially made or owed to Impax under the DCA do not constitute fair value for any services, rights, and/or benefits owed to, rendered on behalf of, or bestowed upon Endo under the DCA, state with specificity the factual basis for Your contention.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will

disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. The question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 6: State with specificity the factual basis for Your allegation that the relevant market "is no broader than extended-release oxymorphone ('oxymorphone ER') tablets approved by the FDA for sale in the United States" (Complaint ¶ 85), including without limitation all facts, Documents, Communications, data, reports, analyses, or other sources or materials that support or otherwise relate to the exclusion of oxycodone, hydrocodone, hydromorphone, morphine sulfate, methadone, buprenorphine, fentanyl, tapentadol, and/or any other opioid product from Your alleged relevant market.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court.

Interrogatory No. 7: State with specificity all facts that Impax and Endo were or reasonably could have been aware of on June 8, 2010, that in any way indicated (i) that Endo's sales of original Opana ER might grow at an annualized rate of over 60 percent from June 2010 through the end of 2011; (ii) that Endo would receive FDA approval of any NDA for a reformulated version of Opana ER; (iii) if Endo received FDA approval of any NDA for a reformulated version of Opana ER, when that approval would occur; or (iv) that Endo would experience a disruption in the supply of original Opana ER due to the shutdown of a Novartis plant in 2012.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the

Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed.

Interrogatory No. 8: If You contend that the SLA and/or DCA caused Impax to launch its generic Opana ER product later than Impax otherwise would have, state with specificity the factual basis for Your contention.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. The question is not whether the payment "caused Impax to launch its generic Opana ER product later than Impax otherwise would have." Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 9: If You contend that consumers would have been better off in the absence of the SLA and/or DCA, state with specificity the factual basis for Your contention.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the

Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. It is not necessary to reconstruct the hypothetical world absent the anticompetitive conduct. Instead, the relevant inquiry is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 10: If You contend that the SLA and/or DCA was anticompetitive, identify and state with specificity the factual basis for each purported anticompetitive effect of the SLA and/or DCA.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court.

Interrogatory No. 11: If You contend that Impax would have launched generic Opana ER "at-risk" in the absence of the SLA and/or DCA, state with specificity the factual basis for Your contention, including without limitation (i) the date on which Impax purportedly would have launched "at-risk"; (ii) all facts showing that Impax had or could have manufactured, packaged, and labeled sufficient quantities of its generic Opana ER product to sustain a launch; (iii) all facts showing that Impax's "at-risk" sales of generic Opana ER would not have been enjoined by any court; and (iv) all facts showing that Impax would have prevailed against Endo in patent litigation.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will

disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. The question is not whether "Impax would have launched generic Opana ER 'at-risk' in the absence of the SLA and/or DCA." Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Interrogatory No. 12: If You contend that Impax could have launched generic Opana ER free from patent risk before January 1, 2013 in the absence of the SLA and/or DCA, state with specificity the factual basis for Your contention, including without limitation (i) the date on which Impax purportedly could have launched generic Opana ER free from patent risk; and (ii) how Impax purportedly could have secured the right to launch generic Opana ER free from patent risk.

Response: Complaint Counsel objects that responding to this Interrogatory involves an opinion or contention that relates to fact or the application of law to fact. Therefore, under the Federal Trade Commission Rules of Practice § 3.35(b)(2), such an interrogatory need not be answered until after designated discovery has been completed. Complaint Counsel further objects that this Interrogatory may call for expert analysis and discovery. Complaint Counsel will disclose any opinions of any testifying experts at the time and in the manner required by the Federal Trade Commission Rules of Practice and the orders of this Court. Complaint Counsel also objects that this Interrogatory mischaracterizes the relevant inquiry. The question is not whether "Impax could have launched generic Opana ER free from patent risk before January 1, 2013 in the absence of the SLA and/or DCA." Instead, the question is whether the payment is larger than avoided litigation costs and sufficient to induce Impax to abandon its patent challenge and eliminate the risk of competition until January 2013.

Dated: June 29, 2017

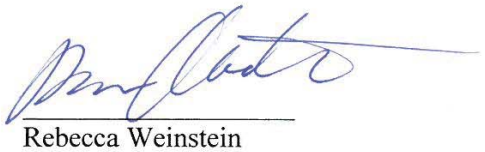
Bradley S. Albert
Charles A. Loughlin
Synda Mark

Counsel Supporting the Complaint
Bureau of Competition
Federal Trade Commission
Washington, D.C. 20024

Certificate of Service

I hereby certify that on June 29, 2017, I served the above Complaint Counsel's Objections and Responses to Respondent Impax Laboratories, Inc.'s First Set of Interrogatories to Complaint Counsel via email on:

Edward D. Hassi
O'Melveny & Myers LLP
1625 Eye Street, NW
Washington, D.C. 20006
ehassi@omm.com



Rebecca Weinstein

Counsel Supporting the Complaint
Bureau of Competition
Federal Trade Commission
Washington, D.C. 20024

EXHIBIT FF

REDACTED IN ENTIRETY

EXHIBIT GG

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	
v.	)	C. A. No. _____
IMPAX LABORATORIES, INC.,	)	
Defendant.	)	

COMPLAINT

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest"), for their Complaint against defendant Impax Laboratories, Inc. ("Impax"), allege as follows.

PARTIES

1. Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceutical company engaged in the research, development, sale and marketing of prescription pharmaceuticals used primarily to treat and manage pain, including OPANA® ER.

2. Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. Penwest is a drug development company focused primarily on the identification, development and commercialization of products for diseases of the nervous system using its expertise in drug development and drug delivery technology, including the extended-release technology used in OPANA® ER.

3. Upon information and belief, Impax is a Delaware corporation, having its principal place of business at 30831 Huntwood Avenue, Hayward, California 94544.

4. Upon information and belief, Impax is manufacturing generic drug products for sale and use throughout the United States, including in this judicial district.

NATURE OF ACTION

5. This is an action for infringement of United States Patent Nos. 5,662,933 ("the '933 patent") and 5,958,456 ("the '456 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100, *et seq.*

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

FACTUAL BACKGROUND

7. On September 2, 1997, the U.S. Patent and Trademark Office ("PTO") duly and legally issued the '933 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. Edward Mendell Co., Inc. was renamed Penwest Pharmaceuticals Co. on October 20, 1997. A true and correct copy of the '933 patent is attached as Exhibit A.

8. On September 28, 1999, the PTO duly and legally issued the '456 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. A true and correct copy of the '456 patent is attached as Exhibit B.

9. Penwest is the assignee and owner of the '933 and '456 patents, and Endo is an exclusive licensee of these patents in the relevant field of use pursuant to a strategic alliance agreement with Penwest.

10. On June 22, 2006, the United States Food and Drug Administration (the "FDA") approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which

contain oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

11. On October 19, 2007, Endo submitted information regarding the '933 and '456 patents to the FDA for listing in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book"), with respect to OPANA® ER tablets. The FDA thereafter listed the '933 and '456 patents in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

12. Upon information and belief, prior to October 2007, Impax submitted to the FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of oxymorphone hydrochloride extended-release tablets, as generic versions of OPANA® ER tablets.

13. Upon information and belief, although the FDA initially accepted Impax's ANDA for substantive review, it thereafter rescinded that acceptance.

14. Upon information and belief, Impax subsequently amended its ANDA.

15. Upon information and belief, by letter dated December 12, 2007, the FDA advised Impax that its ANDA 79-087 "has been deemed acceptable for filing and substantive review by FDA as of November 23, 2007." The FDA's letter also requested that IMPAX provide the notice and information required by 21 U.S.C. §§ 355(j)(2)(B)(i).

16. On December 13, 2007, Impax sent Penwest and Endo a notice stating that it had submitted ANDA No. 79-087 seeking approval to manufacture, use, or sell generic

oxymorphone hydrochloride extended-release tablets prior to the expiration of the '933 and '456 patents (the "Impax Notice").

17. The Impax Notice advised Penwest and Endo that Impax's ANDA included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "paragraph IV certification") that, in Impax's opinion, the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '933 or '456 patents.

18. In the Impax Notice, Impax did not assert that either patent is invalid.

COUNT I

INFRINGEMENT OF THE '456 PATENT

19. Plaintiffs incorporate each of the preceding paragraphs 1 to 18 as if fully set forth herein.

20. Impax's submission of an amended ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A).

21. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '456 patent.

22. Upon information and belief, Impax was aware of the existence of the '456 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '456 patent constitutes infringement of that patent. This is an exceptional case.

COUNT II

INFRINGEMENT OF THE '933 PATENT

23. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

24. Impax's submission of an amended ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '933 patent under 35 U.S.C. § 271(e)(2)(A).

25. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '933 patent.

26. Upon information and belief, Impax was aware of the existence of the '933 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '933 patent constitutes infringement of that patent. This is an exceptional case.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Impax has infringed the '456 patent;

B. A judgment that Impax has infringed the '933 patent;

C. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Impax's ANDA No.79-087 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), shall not be earlier than the expiration date of the '456 and '933 patents, including any extensions;

D. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Impax, its officers, agents, servants and employees, and those persons in active

concert or participation with any of them, from infringement of the '456 and '933 patents for the full terms thereof, including any extensions; and

E. A declaration that this is an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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January 25, 2008