IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA L.P., THE P.F. LABORATORIES, INC. and PURDUE PHARMACEUTICALS L.P., Plaintiffs, v. KV PHARMACEUTICAL COMPANY and ACTAVIS TOTOWA LLC, Defendants.	Civil Action No. _____

COMPLAINT

Plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc. and Purdue Pharmaceuticals L.P., for their Complaint herein, aver as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code.

JURISDICTION AND VENUE

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a) and 2201.

3. This Court has personal jurisdiction over defendants because defendants reside in and, upon information and belief, are doing business in this Judicial District.

4. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

THE PARTIES

5. Plaintiff Purdue Pharma L.P. ("Purdue Pharma") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431. Purdue Pharma is an owner by assignment of the patents in suit identified in paragraph 10 below, and markets and sells in the United States the controlled-release oxycodone hydrochloride pain relief medication OxyContin® Tablets ("OxyContin®").

6. Plaintiff The P.F. Laboratories, Inc. ("P.F. Labs") is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 700 Union Boulevard, Totowa, New Jersey. P.F. Labs is an owner by assignment of the patents in suit identified in paragraph 10 below and manufactures OxyContin® in the United States.

7. Plaintiff Purdue Pharmaceuticals L.P ("Purdue Pharmaceuticals") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at 4701 Purdue Drive, Wilson, North Carolina 27893. Purdue Pharmaceuticals is an owner by assignment of the patents in suit identified in paragraph 10 below and manufactures OxyContin® in the United States.

8. Upon information and belief, defendant KV Pharmaceutical Company ("KV") is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 2503 South Hanley Road, St. Louis, Missouri 63144. Upon information and belief, KV is currently doing business in this Judicial District by making and shipping into this Judicial District, or using, offering to sell or selling, or causing others to use, offer to sell or sell, pharmaceutical products.

9. Upon information and belief, defendant Actavis Totowa LLC ("Actavis") is a company organized and existing under the laws of the State of Delaware, having a place of business at 4 Taft Road, Totowa, New Jersey 07512. Upon information and belief, Actavis is currently doing business in this Judicial District by making and shipping into this Judicial District, or using, offering to sell or selling, or causing others to use, offer to sell or sell, pharmaceutical products.

THE PATENTS IN SUIT

10. Plaintiffs are the lawful owners of all right, title and interest in and to the following United States patents, including all right to sue and to recover for past infringement thereof, which patents contain one or more claims covering the composition and method of use of OxyContin®:

A. United States Patent No. 5,508,042, entitled "CONTROLLED RELEASE OXYCODONE COMPOSITIONS" ("the'042 patent"), a copy of which is attached hereto as Exhibit A, which was duly and legally issued on April 16, 1996 naming Benjamin Oshlack, Mark Chasin, John J. Minogue and Robert F. Kaiko as the inventors;

B. United States Patent No. 5,656,295, entitled "CONTROLLED RELEASE OXYCODONE COMPOSITIONS" ("the '295 patent"), a copy of which is attached hereto as Exhibit B, which was duly and legally issued on August 12, 1997 naming Benjamin Oshlack, Mark Chasin, John J. Minogue and Robert F. Kaiko as the inventors;

C. United States Patent No. 5,549,912, entitled "CONTROLLED RELEASE OXYCODONE COMPOSITIONS" ("the '912 patent"), a copy of which is attached hereto as Exhibit C, which was duly and legally issued on August 27, 1996 naming Benjamin Oshlack, Mark Chasin, John J. Minogue and Robert F. Kaiko as the inventors.

KV'S ANDA

11. Upon information and belief, KV submitted Abbreviated New Drug Application ("ANDA") No. 78-506 to the U.S. Food and Drug Administration ("FDA"), 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 Oxycodone Hydrochloride Extended-Release Tablets 10 mg, 20 mg, 40 mg and 80 mg ("KV's Tablets"), a generic version of Purdue's OxyContin®, before the expiration of the '042, '295 and '912 patents.

12. Upon information and belief, KV's ANDA contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the '042, '295 and '912 patents are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of KV's Tablets.

13. In a letter dated December 6, 2006 addressed to the plaintiffs, KV sent "notice" with respect to its 10 mg, 20 mg, 40 mg and 80 mg Tablets and the '042, '295 and '912 patents as provided by 21 U.S.C. § 355(j)(2)(B)(ii) ("KV's notice"). The plaintiffs received KV's notice on or about December 11, 2006.

14. KV's notice does not provide any valid basis for concluding that the '042, '295 and '912 patents are invalid, unenforceable and/or not infringed.

15. Upon information and belief, the composition and method of use of KV's Tablets are covered by one or more claims of the '042, '295 and '912 patents.

16. Upon information and belief, KV's submission of its ANDA was an act of infringement of the '042, '295 and '912 patents under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

17. Upon information and belief, KV's commercial manufacture, use, sale and/or offer for sale of its Tablets would infringe, contribute to the infringement of, and induce the infringement of one or more claims of the '042, '295 and '912 patents.

18. Upon information and belief, KV has been aware of the existence of the '042, '295 and '912 patents, and has no reasonable basis for believing that KV's Tablets will not infringe the '042, '295, and '912 patents, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

19. The acts of infringement by KV set forth above will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

ACTAVIS' ANDA

20. Upon information and belief, Actavis submitted ANDA No. 78-507 to the FDA, 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 Oxycodone Hydrochloride Extended-Release Tablets 10 mg, 20 mg, 40 mg and 80 mg ("Actavis' Tablets"), a generic version of Purdue's OxyContin®, before the expiration of the '042 patent.

21. Upon information and belief, Actavis' ANDA contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the '042 patent is invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Actavis' Tablets.

22. In a letter dated December 4, 2006 addressed to the plaintiffs, Actavis sent "notice" with respect to the '042 patent as provided by 21 U.S.C. § 355(j)(2)(B)(ii) ("Actavis' notice"). The plaintiffs received Actavis' notice between December 6 and 11, 2006.

23. Actavis' notice does not provide any valid basis for concluding that the '042 patent is invalid, unenforceable and/or not infringed.

24. Upon information and belief, the method of use of Actavis' Tablets is covered by one or more claims of the '042 patent.

25. Upon information and belief, Actavis' submission of its ANDA was an act of infringement of the '042 patent under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

26. Upon information and belief, Actavis' commercial manufacture, use, sale and/or offer for sale of Actavis' Tablets would infringe, contribute to the infringement of, and induce the infringement of one or more claims of the '042 patent.

27. Upon information and belief, Actavis has been aware of the existence of the '042 patent and has no reasonable basis for believing that Actavis' Tablets will not infringe the '042 patent, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

28. The acts of infringement by Actavis set forth above will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

WHEREFORE, plaintiffs pray for judgment:

A. Adjudging that KV has infringed the '042, '295 and '912 patents, and that the commercial sale, offer for sale, and/or manufacture of KV's Tablets would infringe, induce infringement of, and contribute to the infringement of the '042, '295 and '912 patents;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of KV's ANDA No. 78-506, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date which is not earlier than the last date of expiration of the '042, '295 and '912 patents;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., KV, its officers, agents, servants,

employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities and all other persons acting in concert, participation or in privity with it, and its successors and assigns, from any commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States, of any drug product that infringes the '042, '295 or '912 patent;

D. Adjudging that defendant Actavis has infringed the '042 patent, and that the commercial sale, offer for sale and/or manufacture of Actavis' Tablets would infringe, induce infringement of, and contribute to the infringement of the '042 patent;

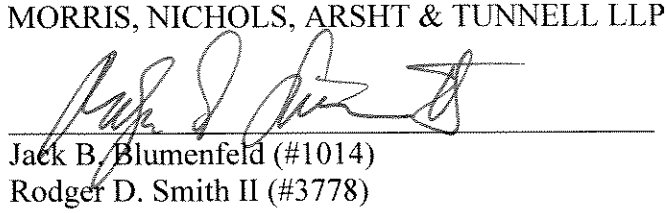
E. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Actavis' ANDA No. 78-507, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date that is not earlier than the date of expiration of the '042 patent;

F. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Actavis, its officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities and all other persons acting in concert, participation or in privity with it, and its successors and assigns, from any commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States, of any drug product that infringes the '042 patent;

G. Declaring this an exceptional case and awarding plaintiffs their attorneys fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

H. Awarding plaintiffs such other and further relief as this Court may deem just and proper.

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January 16, 2007

EXHIBIT A

US005508042A

United States Patent [19]

Oshlack et al.

[11] **Patent Number: 5,508,042**

[45] **Date of Patent: Apr. 16, 1996**

[54] **CONTROLLED RELEASE OXYCODONE COMPOSITIONS**

[75] Inventors: **Benjamin Oshlack**, New York, N.Y.; **Mark Chasin**, Manalpan, N.J.; **John J. Minogue**, Mount Vernon, N.Y.; **Robert F. Kaiko**, Weston, Conn.

[73] Assignee: **Euro-Celtigue, S.A.**, Luxembourg, Luxembourg

[21] Appl. No.: **467,584**

[22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

[60] Division of Ser. No. 81,302, Jun. 18, 1993, which is a continuation-in-part of Ser. No. 800,549, Nov. 27, 1991, Pat. No. 5,266,331.

[51] **Int. Cl.**[6] **A61K 9/22**; A61K 9/26

[52] **U.S. Cl.** **424/468**; 424/469; 424/470; 424/486; 424/487; 424/488; 424/494; 424/496; 424/497; 424/498; 424/501; 424/502; 424/495

[58] **Field of Search** 424/486, 464, 424/465, 468–469, 470, 487–488, 49–98, 494

[56] **References Cited**

U.S. PATENT DOCUMENTS

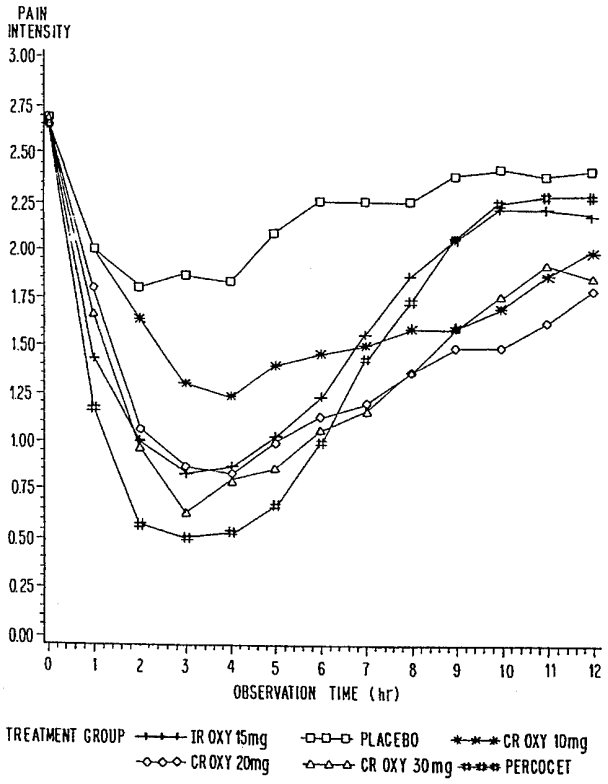
4,862,598	8/1989	Oshlack	424/470
4,990,341	2/1991	Goldie et al.	424/484
5,266,331	11/1993	Oshlack et al.	424/468

Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Steinberg, Raskin & Davidson

[57] **ABSTRACT**

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e. every 12 hour) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients by administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, such that a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions are achieved. Controlled release oxycodone formulations for achieving the above are also disclosed.

2 Claims, 5 Drawing Sheets



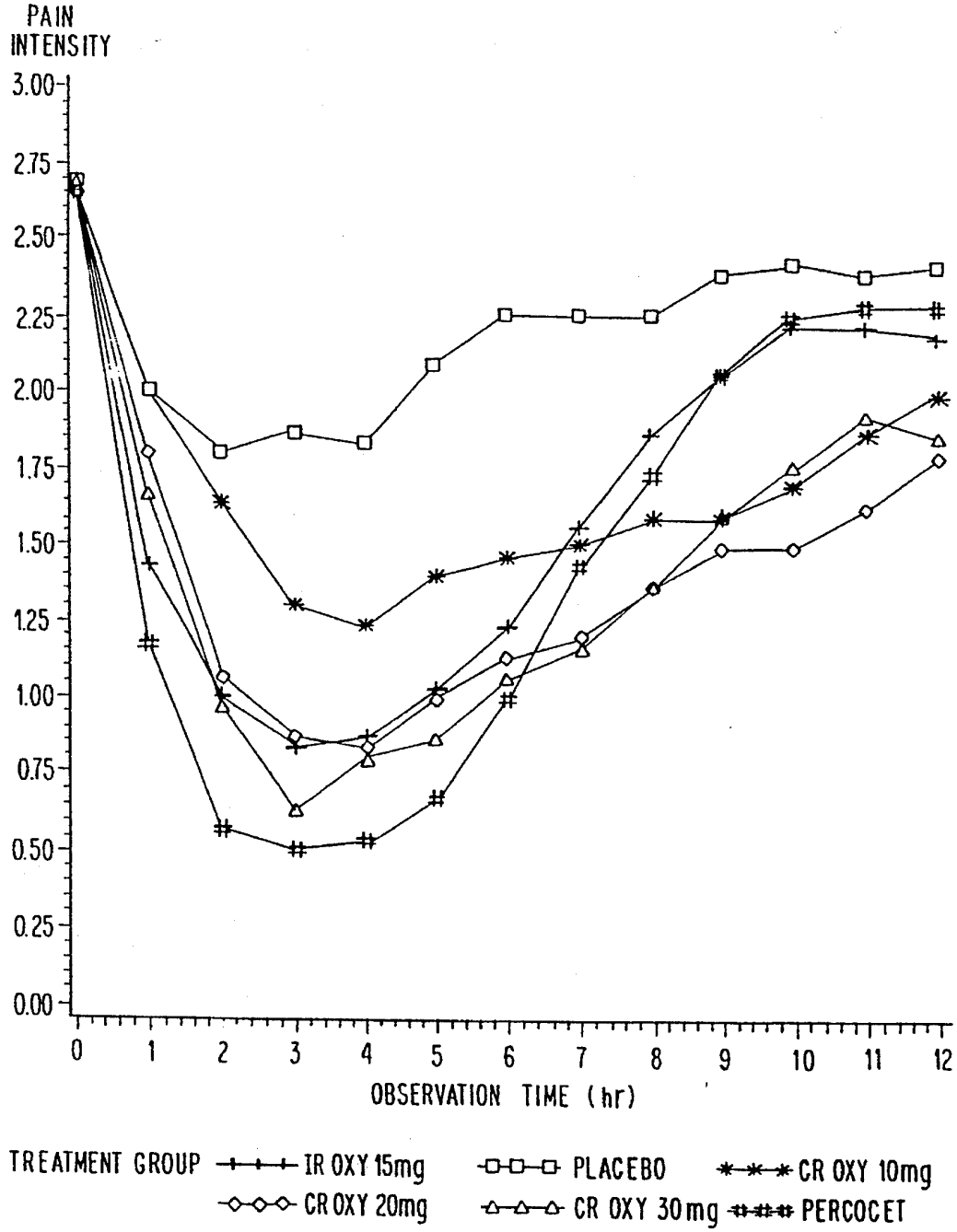

PAIN INTENSITY
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 1

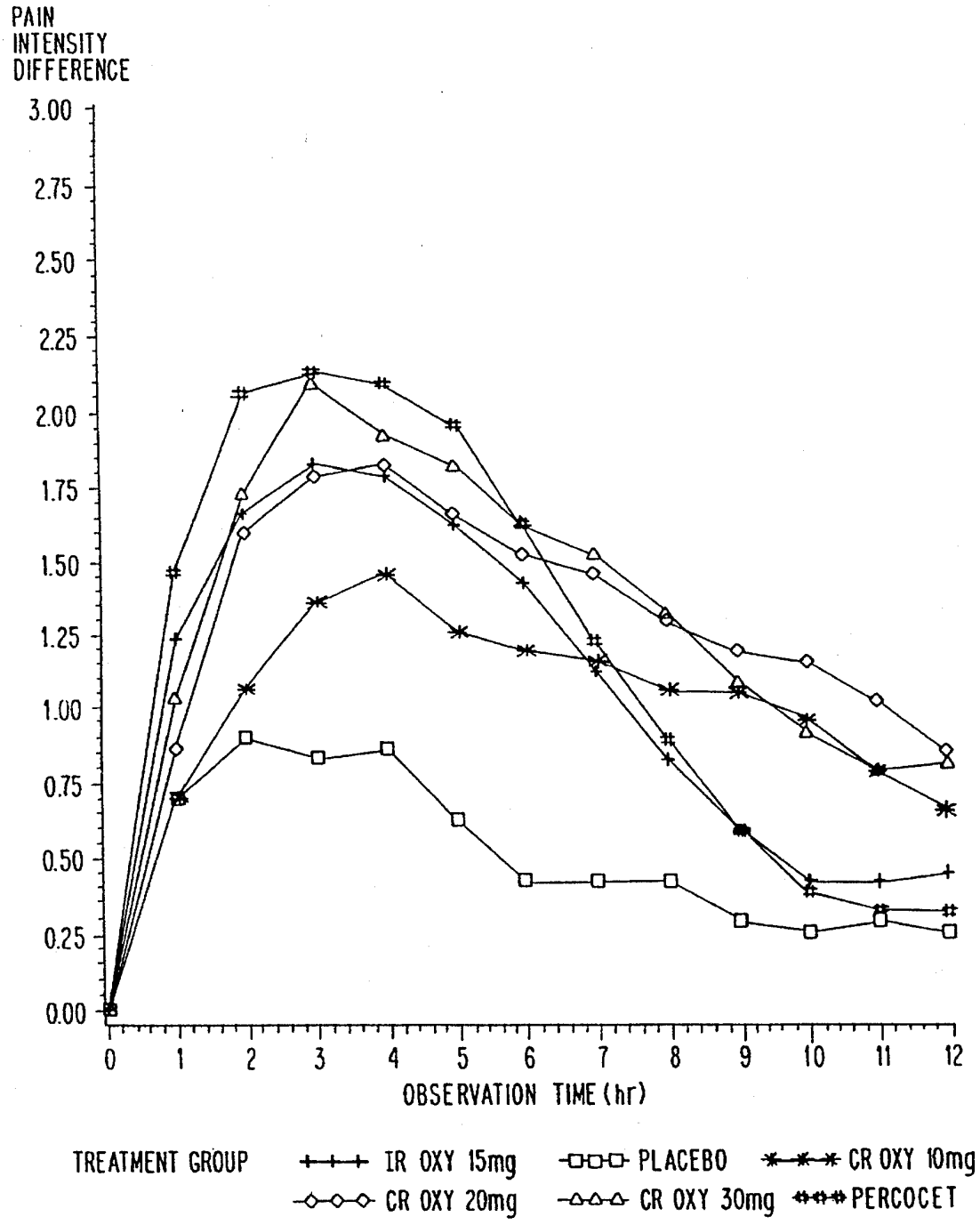

PAIN
INTENSITY
DIFFERENCE
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG.2

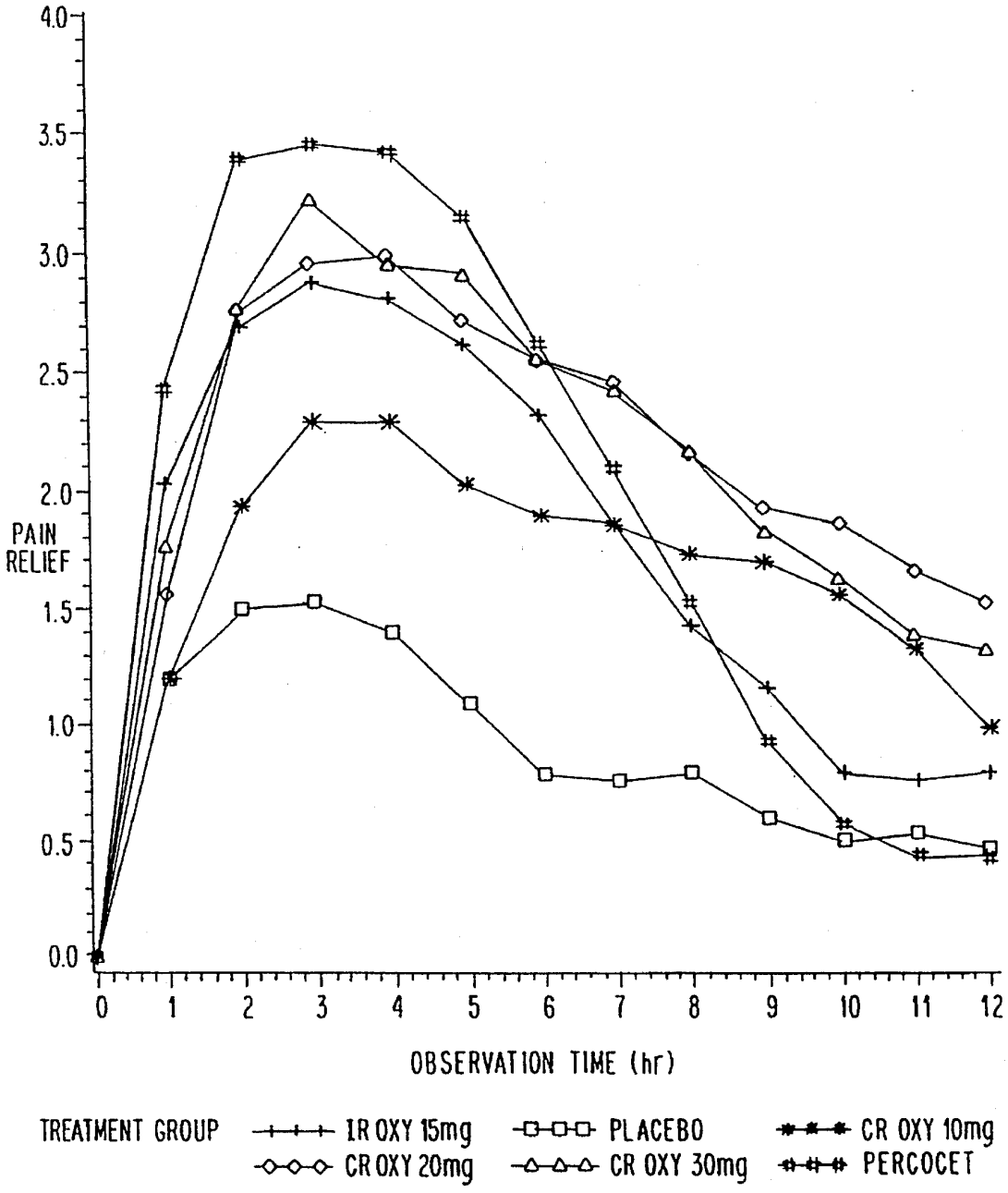

4.0
3.5
3.0
2.5
2.0
PAIN RELIEF
1.5
1.0
0.5
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 3

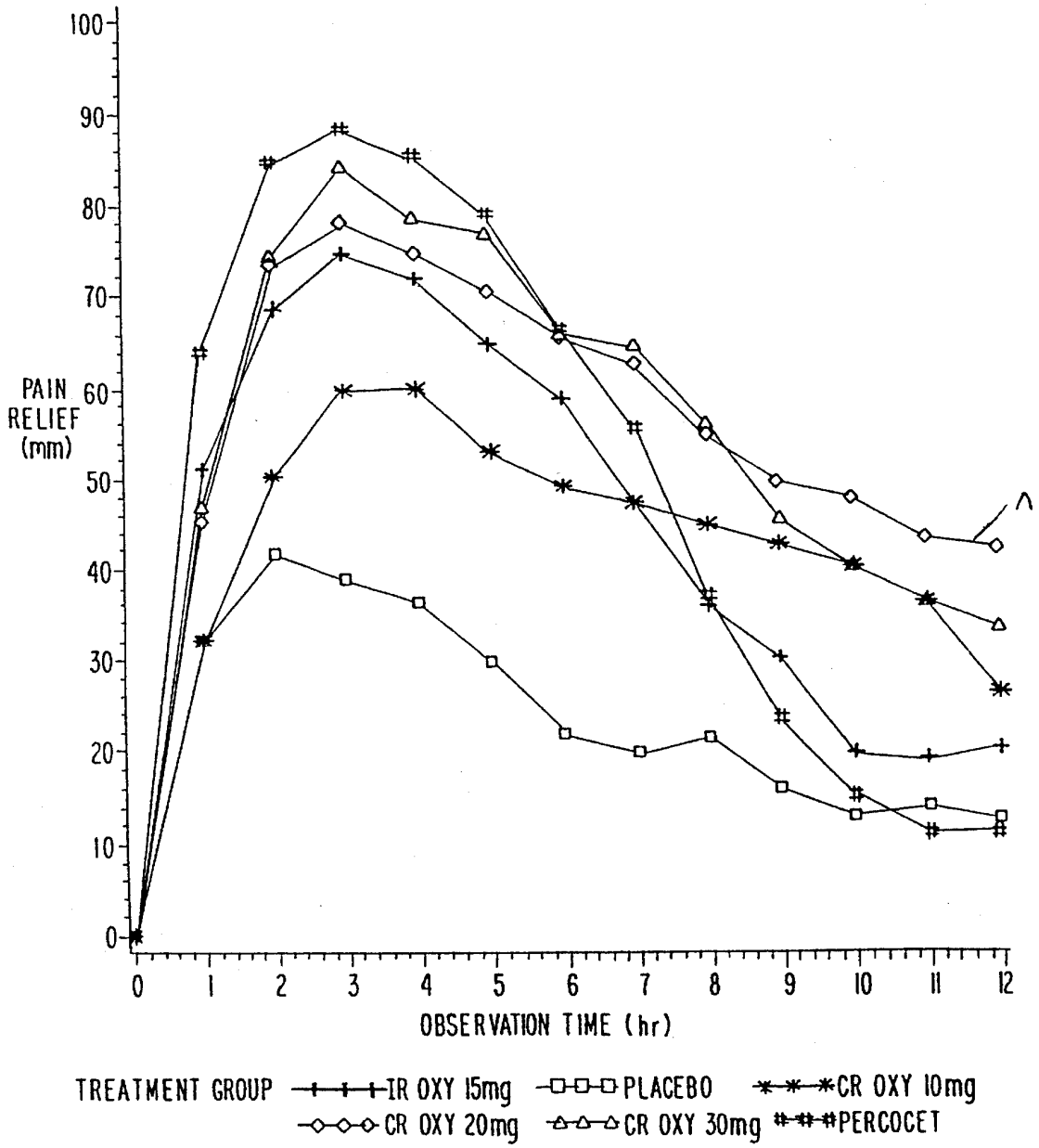

PAIN RELIEF (mm)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 4

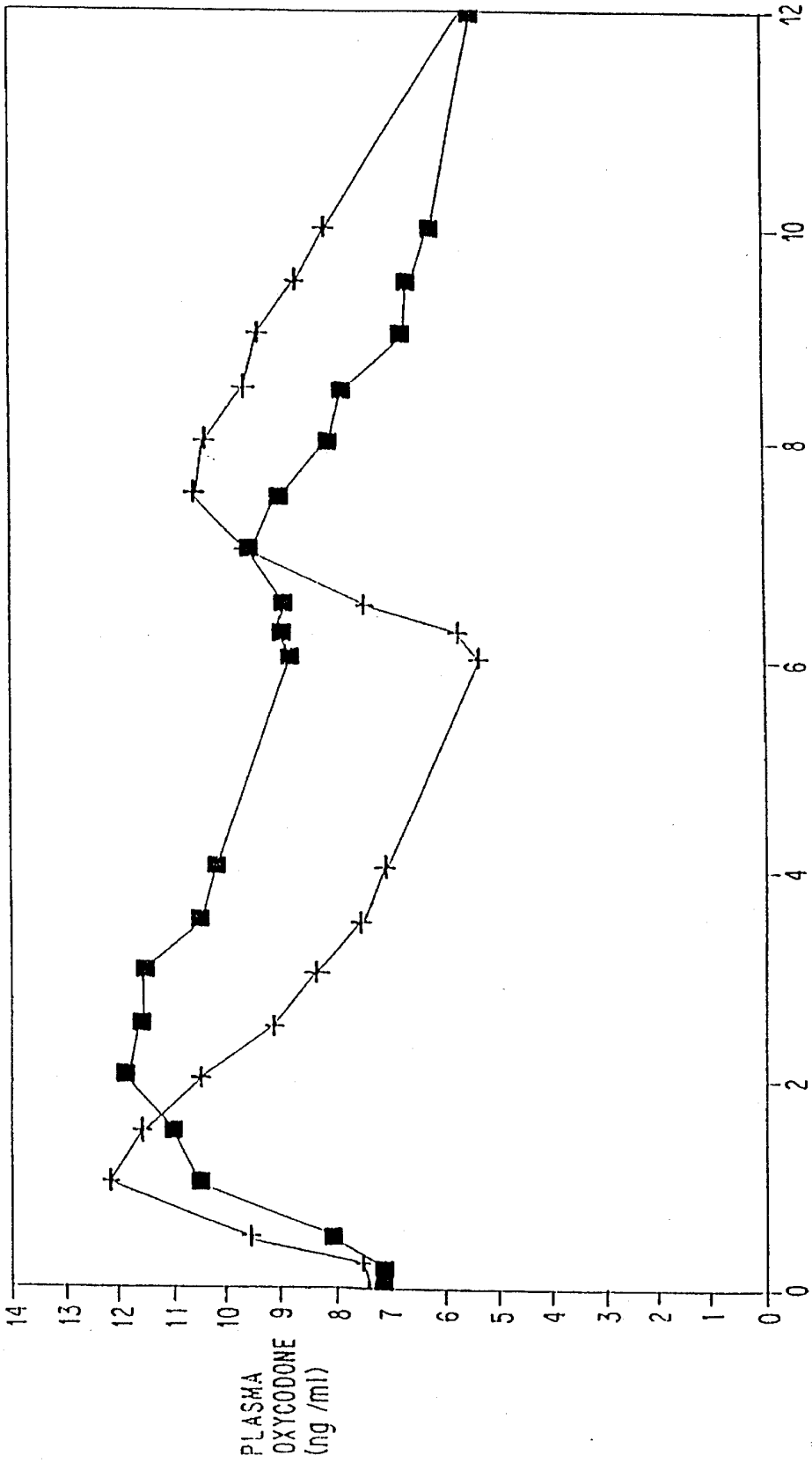

PLASMA OXYCODONE (ng/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
0
2
4
6
8
10
12
TIME FROM LAST DOSE (HRS)
OCAcr
ROX
OCAcr Rox Sol
C(max) 15.1 15.6
AUC(0,12) 103.5 99.1
T(max) 3.2 1.4

FIG. 5

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

This is a divisional of application Ser. No. 08/081,302, filed Jun. 18, 1993, which is a continuation-in-part of U.S. application Ser. No. 07/800,549, filed Nov. 27, 1991, now U.S. Pat. No. 5,266,331.

BACKGROUND OF THE INVENTION

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined. The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions. . . . This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain. . . . Give each analgesic an adequate trial by dose titration . . . before switching to another drug."

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

It has previously been known in the art that controlled release compositions of opioid analgesics such as morphine, hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Pat. No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for substantially improving the efficiency and quality of pain management.

It is another object of the present invention to provide an opioid analgesic formulation which substantially improves the efficiency and quality of pain management.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the approximately eight-fold range in daily dosages required to control pain in approximately 90% of patients.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the variability in daily dosages and formulation requirements necessary to control pain in substantially all patients.

It is yet another object of the present invention to provide a method for substantially reducing the time and resources need to titrate patients requiring pain relief on opioid analgesics.

It is yet another object of the present invention to provide controlled release opioid formulations which have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects.

The above objects and others are attained by virtue of the present invention, which is related to a solid controlled release oral dosage form, the dosage form comprising from about 10 to about 40 mg of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH, such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4.5 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "substantially independent of pH" means that the difference, at any given time, between the amount of oxycodone released at, e.g., pH 1.6, and the amount released at any other pH, e.g., pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer), is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 to about 40 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after

administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising up to about 160 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIGS. **1–4** are graphs showing the time-effect curves for pain intensity differences and pain relief for Example 17;

FIG. **5** is a graph showing the mean plasma oxycodone concentration for a 10 mg controlled release oxycodone formulation prepared in accordance with the present invention and a study reference standard.

DETAILED DESCRIPTION

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

The use of from about 10 mg to about 40 mg of 12-hourly doses of controlled-release oxycodone to control pain in approximately 90% of patients relative to a wider dosage range of other mμ-agonist analgesics, indicated for moderate to severe pain, is an example of the unique characteristics of the present invention. It should also be appreciated that the remaining 10% of patients would also be successfully managed with 12-hourly controlled-release oxycodone over a relatively narrower dosage range than with the use of other similar analgesics. Substantially all of those remaining 10% of patients not managed with controlled release oxycodone, 10 mg to 40 mg every 12 hours, would be managed using dosages of greater than 40 mg every 12 hours through 160 mg every 12 hours utilizing any one of a number or multiples of formulation strengths such as 10, 20, 40, 80 and 160 mg unit dosages or combinations thereof. In contrast, the use of other similar analgesics such as morphine would require a wider range of dosages to manage the remaining 10% of patients. For example, daily dosages of oral morphine equivalents in the range of 1 gram to more than 20 grams have been observed. Similarly, wide dosage ranges of oral hydromorphone would also be required.

Morphine, which is considered to be the prototypic opioid analgesic, has been formulated into a 12 hour controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Pharma, L.P.). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately ½ the dosage range as compared to commercially available controlled release morphine formulations (such as MS Contin®) to control 90% of patients with significant pain.

Repeated dose studies with the controlled release oxycodone formulations administered every 12 hours in comparison with immediate release oral oxycodone administered every 6 hours at the same total daily dose result in comparable extent of absorption, as well as comparable maximum and minimum concentrations. The time of maximum concentration occurs at approximately 2–4.5 hours after oral administration with the controlled-release product as compared to approximately 1 hour with the immediate release product. Similar repeated dose studies with MS Contin® tablets as compared to immediate release morphine provide for comparable relative results as with the controlled release oxycodone formulations of the present invention.

There exists no substantial deviation from parallelism of the dose-response curves for oxycodone either in the forms of the controlled release oxycodone formulations of the present invention, immediate release oral oxycodone or parenteral oxycodone in comparison with oral and parenteral opioids with which oxycodone has been compared in terms of dose-response studies and relative analgesic potency assays. Beaver, et al., "Analgesic Studies of Codeine and Oxycodone in Patients with Cancer. II. Comparisons of Intramuscular Oxycodone with Intramuscular Morphine and Codeine", J. Pharmacol. and Exp. Ther., Vol. 207, No. 1, pp. 101–108, reported comparable dose-response slopes for parenteral oxycodone as compared to parenteral morphine and comparable dose-response slopes for oral as compared to parenteral oxycodone.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mμ-agonist analgesic to another regardless of the dosage of the former. Unless the dose-response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

It is further clinically significant that a dose of about 80 mg controlled release oxycodone administered every 12

hours will provide acceptable pain relief management in, e.g., approximately 95% of patients with moderate to severe pain, and that about 160 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately all patients with moderate to severe pain.

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4–8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2–4.5 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of up to 2 hours after administration.

A further advantage of the present composition, which releases oxycodone at a rate that is substantially independent of pH, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 500 mg, most especially between 10 and 160 mg, of oxycodone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, 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 polymer.

(b) 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. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these 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.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

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, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. 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 oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15% (by wt) of the at least one hydroxyalkyl cellulose.

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 oxycodone 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 preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit® RS PM, commercially available from Rohm Pharma.

In the present preferred dosage form, 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 considerable extent, the release rate of the oxycodone from the formulation. A ratio 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, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

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

In addition to the above ingredients, a controlled 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.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70%

and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising 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 hydroxy propyl 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.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating hydromorphone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}–C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

(a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronising agent,

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets—Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit® RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1

Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	% (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	213.75	57
Eudragit ® RS PM	45.0	12
Purified Water	q.s*	—
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37° C., 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5

TABLE 2-continued

Dissolution of Oxycodone 30 mg Controlled Release Tablets	
Time	% Oxycodone Dissolved
4	58.2
8	73.2
12	81.8
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets—Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30° C.; and then passed through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30° C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 (10 mg controlled release oxycodone) is set forth in Table 3 below:

TABLE 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets		
Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit ® RS PM	15.00	12
Ethanol	q.s.*	—
Purified Water	q.s.*	—
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric (pH 1.2) then changed to 900 ml at pH 7.5.

The results are set forth in Table 4 below:

TABLE 4

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLES 3–4

Controlled Release Oxycodone 10 and 20 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70° C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

TABLE 5

Formula of Controlled Release Oxycodone 10 mg Tablets		
Component	Mg/Tablet	% (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit ® RS 30D (solids)	10.0*	8.0
Triacetin ®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit ® RS 30D Aqueous dispersion is equivalent to 10 mg of Eudragit ® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 6 below:

TABLE 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

The formula for the tablets of Example 4 is set forth in Table 7 below:

TABLE 7

Formula of Controlled Release Oxycodone 20 mg Tablets

Component	Mg/Tablet
Oxycodone Hydrochloride	20.0
Lactose (spray dried)	59.25
Povidone	5.0
Eudragit ® RS 30D (solids)	10.0*
Triacetin ®	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total:	125.0

The tablets of Example 4 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 8 below:

TABLE 8

Dissolution of Oxycodone 20 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	31
2	44
4	57
8	71
12	79
18	86
24	89

EXAMPLES 5–6

In Example 5, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 6, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 5 and 6 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 9 and 10 below:

TABLE 9

Example 5
Percentage Oxycodone HCl 30 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

TABLE 10

Example 6
Percentage Oxycodone HCl - 10 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 7–12

In Examples 7–12, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,990,341.

In Example 7, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 8 is prepared in the same manner as Example 7; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 7 and 8 are set forth in Tables 11 and 12, respectively.

TABLE 11

Formulation of Example 7

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 12

Formulation of Example 8

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5

TABLE 12-continued

Formulation of Example 8		
Ingredient	mg/tablet	g/batch
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 9, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Pat. No. 4,990,341. The method of manufacture is the same as set forth in Examples 7 and 8 above. Example 10 is prepared according to Example 9, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 9 and 10 are set forth in Tables 13 and 14, respectively.

TABLE 13

Formulation of Example 9		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 14

Formulation of Example 14		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 11, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. Pat. No. 4,990,341.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C. and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 12 is prepared in identical fashion to Example 11, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 11 and 12 are set forth in Tables 15 and 16, respectively.

TABLE 15

Formulation of Example 11		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

TABLE 16

Formulation of Example 12		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 7–12 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 17.

TABLE 17

DISSOLUTION STUDIES OF EXAMPLES 7–12						
Time	% Oxycodone Dissolved					
(hrs)	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 13–16

Clinical Studies

In Examples 13–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 13, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 14, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 15, a single dose study was conducted on 22 subjects using oxycodone tablets prepared according to Example 3, and compared to a 20 mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3×10 mg oxycodone tablets prepared according to Example 3, and compared to a 30 mg oxycodone immediate release solution.

The results of Examples 13–16 are set forth in Table 18.

TABLE 18

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
13	10 mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
14	5 mg IR q6h	121	17	1.2
	10 mg CR q12h	130	17	3.2
15	20 mg IR	188	40	1.4
	2 × 10 mg CR	197	18	2.6
16	30 mg IR	306	53	1.2
	3 × 10 mg CR	350	35	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

EXAMPLE 17

Clinical Studies

In Example 17, a single dose, double blind, randomized study determined the relative analgesic efficacy, the acceptability, and relative duration of action of an oral administration of controlled release oxycodone 10, 20 and 30 mg prepared according to the present invention (CR OXY) compared to immediate release oxycodone 15 mg (IR OXY), immediate release oxycodone 10 mg in combination with acetaminophen 650 mg (IR OXY/APAP) and placebo in 180 patients with moderate or severe pain following abdominal or gynecological surgery. Patients rated their pain intensity and pain relief hourly for up to 12 hours postdosing. Treatments were compared using standard scales for pain intensity and relief, and onset and duration of pain relief.

All active treatments were significantly superior to placebo for many of the hourly measures, and for sum pain intensity differences (SPID) and total pain relief (TOTPAR). A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak pain intensity difference (PID), with CR OXY 20 mg and 30 mg being significantly better than the 10 mg dose. IR OXY was significantly superior to CR OXY 10 mg at hr 1 and 2. IR OXY/APAP was significantly superior to the 3 doses of CR OXY at hr 1, and to CR OXY 10 mg at hrs 2 through 5. Onset time was significantly shorter for the IR OXY and IR OXY/APAP treatment groups in comparison to the 3 CR OXY treatments. The distribution functions for duration of relief revealed significantly longer duration of relief for the three CR OXY doses than for IR OXY and IR OXY/APAP. No serious adverse experiences were reported. The results are more particularly reported in Table 19 below.

TABLE 19

	PATIENT DISPOSITION						
	TREATMENT GROUP						
	IR OXY		CR OXY				
	15 mg	PLACEBO	10 mg	20 mg	30 mg	2 PERC*	TOTAL
Enrolled and Randomized to Study Treatment	31	31	30	30	30	30	182
Entered the Study Treatment Phase	31	31	30	30	30	30	182
Completed the Study	31	30	30	30	30	30	181
Discontinued from the Study	0	1	0	0	0	0	1
Excluded from Efficacy Analysis	0	1	0	0	0	0	1
Vomited prior to 1 hr post dose	1	0	0	0	0	0	1
Inadvertently received rescue during study							
Analysis Population:							
Evaluable for Safety and Efficacy	30	30	30	30	30	30	180
Evaluable for Safety	31	31	30	30	30	30	182

*2 tablets of Percocete ®

The time-effect curves for pain intensity, pain intensity differences and pain relief are shown in FIGS. 1–4. CR OXY 10 mg had significantly ($p<0.05$) lower pain intensity scores than the placebo-treated patients at hours 3–11 and lower pain scores than IR OXY 15 mg and Percocet® at hour 10. CR OXY 20 mg has significantly ($p<0.05$) lower pain intensity scores compared to placebo at hours 2–11 and significantly ($p<0.05$) lower pain scores than CR OXY 10 mg, IR OXY 15 mg and Percocet at hours 9–11. CR OXY 30 mg had significantly ($p<0.05$) lower pain scores than placebo at hours 2–11 and lower pain scores than CR OXY 10 mg at hours 2, 3, and 5 and lower scores than Percocet® at hour 10.

For hourly pain relief scores categorical and visual analog scales (CAT and VAS), CR OXY 10 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 3–11 and higher relief scores than IR OXY and Percocet® at hour 10 (and Percocet® at hour 11). CR OXY 20 mg had significantly ($p<0.05$) higher relief scores than placebo at hours 2–12 and higher relief scores than Percocet® at hours 9–12. In addition, CR OXY had significantly ($p<0.05$) higher pain relief than IR OXY at hours 10–12. CR OXY 30 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 2–12 and higher scores than Percocet® at hours 9–12 and IR OXY 15 mg at hour 10.

Each treatment group was significantly ($p<0.05$) better than placebo with respect to the sum of the pain intensity differences (SPID) and total pain relief (TOTPAR).

Duration of pain relief as measured by the patient stopwatch method showed that CR OXY 10 mg, 20 mg and 30 mg had significantly ($p<0.05$) longer duration of action compared to IR OXY 15 mg and 2 tablets Percocet®. In addition, the three controlled-release formulations had significantly ($p<0.05$) longer times to remedication compared to Percocet®.

Before remedication, a total of 104 (57%) of patients reported 120 adverse experiences. The most common were somnolence, fever, dizziness and headache.

Based upon the results of this study it is concluded that the controlled release oxycodone formulations of the present invention relieve moderate to severe post-operative pain, e.g., due to abdominal or gynecological surgery in women. There is a dose response noted in which placebo <10 mg<20 mg<30 mg CR OXY following a single dose. Onset of action occurred in one hour with peak effects noted from 2 to 5 hours and a duration of effect from 10 to 12 hours. In the chronic pain situation steady state dosing may prolong this effect. Side effects are expected and easily managed. Headache may be related to dose. Dizziness and somnolence were reported.

IR OXY 15 mg has an intermediate peak effect compared to controlled release oxycodone. Its duration of action is shorter (6–8 hours). Percocet® is quite effective in terms of onset, peak effect and safety. The duration of action is 6–8 hours.

FIG. **5** shows the mean plasma oxycodone concentrations for the two formulations over the 12 hour dosing interval. The results are summarized in Table 18 in terms of mean values, ratios of mean values and 90% confidence intervals.

As inspection of Table 18 reveals, with one exception, no significant differences were detected between the two formulations. The single exception is the mean t_{max} for CR OXY of 3.18 hours which, as expected for a controlled release formulation, significantly exceeded the ROX mean of 1.38 hours. Mean AUC-based bioavailability, (ROX= 100%) was 104.4% with 90% confidence limits of 90.9 to 117.9%. Thus, the FDA specification of ±20% is met so that the study results support an assertion of equal oxycodone availability.

TABLE 20

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q12H) AND ROXICODONE ® ORAL SOLUTION (5 mg q6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
C_{max} (ng/mL)				
ARITH. MEAN (SD)	15.11(4.69)	15.57(4.41)	97.08	85.59–108.50
GEOMETRIC MEAN	14.43	15.01	95.14	
C_{min} (ng/mL)				
ARITH. MEAN (SD)	6.24(2.64)	6.47(3.07)	96.41	80.15–112.74
GEOMETRIC MEAN	5.62	5.83	96.48	
t_{max} (hrs)	3.18(2.21)	1.38(0.71)*	230.17	160.71–298.71
ARITH. MEAN (SD)				
AUC (0–12 hrs)				
ARITH. MEAN (SD)	103.50(40.03)	99.10(35.04)	104.44	90.92–117.94
GEOMETRIC MEAN	97.06	93.97	103.29	
% Swing	176.36(139.0)	179.0(124.25)	98.53	62.06–134.92
ARITH. MEAN (SD)				
% Fluctuation	108.69(38.77)	117.75(52.47)	92.22	76.81–107.57
ARITH. MEAN (SD)				
End Point	−1.86(2.78)	−1.86(2.19)	99.97	117.77–22.23
ARITH. MEAN (SD)				

*90% Confidence Interval
Significant Difference $p < 0.05$

In summary, CR OXY was clearly an effective oral analgesic, with a slower onset but a longer duration of effect than either IR OXY or IR OXY/APAP.

EXAMPLE 18

Clinical Studies

In Example 18, a steady state crossover trial was conducted in 21 normal male subjects comparing

a. CR OXY 10 mg administered every 12 hours (q12h); and

b. Roxicodone® oral solution 5 mg (ROX) administered every 6 hours (q6h),

Treatment (b) was the study reference standard. The average age was 34 years, height 176 cm and weight 75 kg. No unusual features were noted about the group.

EXAMPLE 19

Clinical Studies

In Example 19, twenty-four normal, healthy male subjects were enrolled in a randomized single-dose two-way crossover study to compare the plasma oxycodone concentrations obtained after dosing with two controlled-release oxycodone 10 mg tablets versus 20 mg (20 ml of 5 mg/5 ml) of immediate release (IR) oxycodone hydrochloride solution. Twenty-three subjects completed the study and were eligible for analysis.

Plasma oxycodone concentrations were determined by a high performance liquid chromatographic procedure. Arithmetic Mean C_{max}, t_{max}, AUC, and half-lives calculated from individual plasma oxycodone concentration-versus-time data are set forth in Table 21:

TABLE 21

Pharmaco-kinetic Parameter	Reference Product IR Oxycodone 20 mg	Test Product CR Oxycodone 2 × 10 mg	F. (%)	90% Confidence Interval
C_{max} (ng/ml)	41.60	18.62	44.75	32.5–57.0
t_{max} (hours)	1.30	2.62	200.83	169.8–232.6
AUC (0–36) (mg × hr/ml)	194.35	199.62	102.71	89.5–115.9
AUC (0–∞) (ng × hr/ml)	194.38	208.93	107.49	92.9–121.9
$t_{½ (elim)}$ (hrs)	3.21	7.98*	249.15	219.0–278.8
$t_{½ (abs)}$ (hrs)	0.35	0.92*	264.17	216.0–310.7

F. % = Oral bioavailability (CR oxycodone 2 × 10 mg/IR oxycodone 20 mg)
*Statistically significant (p = 0.0001)

For C_{max}, t_{max}, $t_{½}$ (elim)and $t_{½}$ (abs)there were statistically significant differences between the CR OXY and IR OXY. There were no statistically significant differences between the two treatments in the extent of absorption [AUC (0,36), AUC (0,∞). The 90% confidence interval for CR OXY relative to IR OXY relative was 89.5%–115.9% for AUC (0,36) and 92.9%–121.9% for AUC (0,∞). Based on the 90% confidence interval analysis, the controlled-release oxycodone tablets were equivalent in extent of absorption (AUC 0,36) to the immediate-release oxycodone solution. The controlled-release oxycodone absorption was slower by approximately 1.3 hours. No statistically significant differences were noted between the two treatments with reference to adverse experiences, none of which were considered clinically unusual for opiates for this type of study.

The above studies demonstrate a significant dose-response relationship utilizing the controlled release oxycodone formulations of the present invention at dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Kaiko R. S., Van Wagoner D., Brown J., et al., "Controlled-Release Oral Morphine (MS Contin® Tablets, MSC) in Postoperative Pain.", Pain Suppl., 5: S149 1990, who compared 30, 60, 90, and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield, et al., "Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations", Clinical Pharmacology & Therapeutics, (in press), who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A method for reducing the range in daily dosages required to control pain in human patients, comprising administering an oral controlled release dosage formulation comprising from about 10 to about 40 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

2. A method for reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 mg to about 160 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

* * * * *

EXHIBIT B

US005656295A

United States Patent [19]

Oshlack et al.

[11] Patent Number: 5,656,295

[45] Date of Patent: *Aug. 12, 1997

[54] **CONTROLLED RELEASE OXYCODONE COMPOSITIONS**

[75] Inventors: **Benjamin Oshlack**, New York, N.Y.; **Mark Chasin**, Manalpan, N.J.; **John Joseph Minogue**, Mount Vernon, N.Y.; **Robert Francis Kaiko**, Weston, Conn.

[73] Assignee: **Euro-Celtique, S.A.**, Luxembourg, Luxembourg

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,266,331.

[21] Appl. No.: **618,344**

[22] Filed: **Mar. 19, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 81,302, Jun. 18, 1993, Pat. No. 5,549,912, which is a continuation-in-part of Ser. No. 800,549, Nov. 27, 1991, Pat. No. 5,266,331.

[51] **Int. Cl.**[6] **A61K 9/22**; A61K 9/26

[52] **U.S. Cl.** **424/468**; 424/469; 424/470; 424/486; 424/487; 424/488; 424/494; 424/496; 424/497; 424/498; 424/501; 424/502; 424/495

[58] **Field of Search** 424/468–470, 424/487–488, 494, 496–498, 464–469

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,862,598	9/1989	Oshlack	424/470
4,990,341	2/1991	Goldie, et al.	424/484
5,266,331	11/1993	Oshlack, et al.	424/468

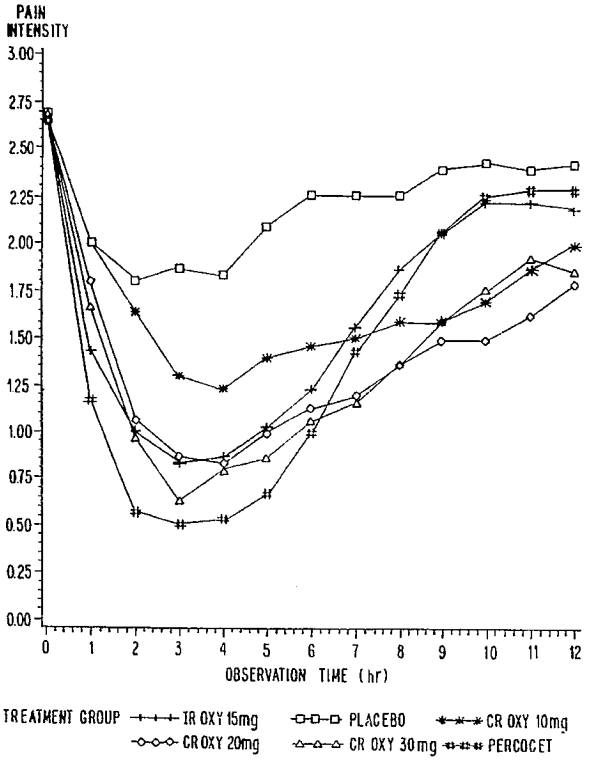
Primary Examiner—Edward J. Webman

Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients by administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, such that a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions are achieved. Controlled release oxycodone formulations for achieving the above are also disclosed.

10 Claims, 5 Drawing Sheets



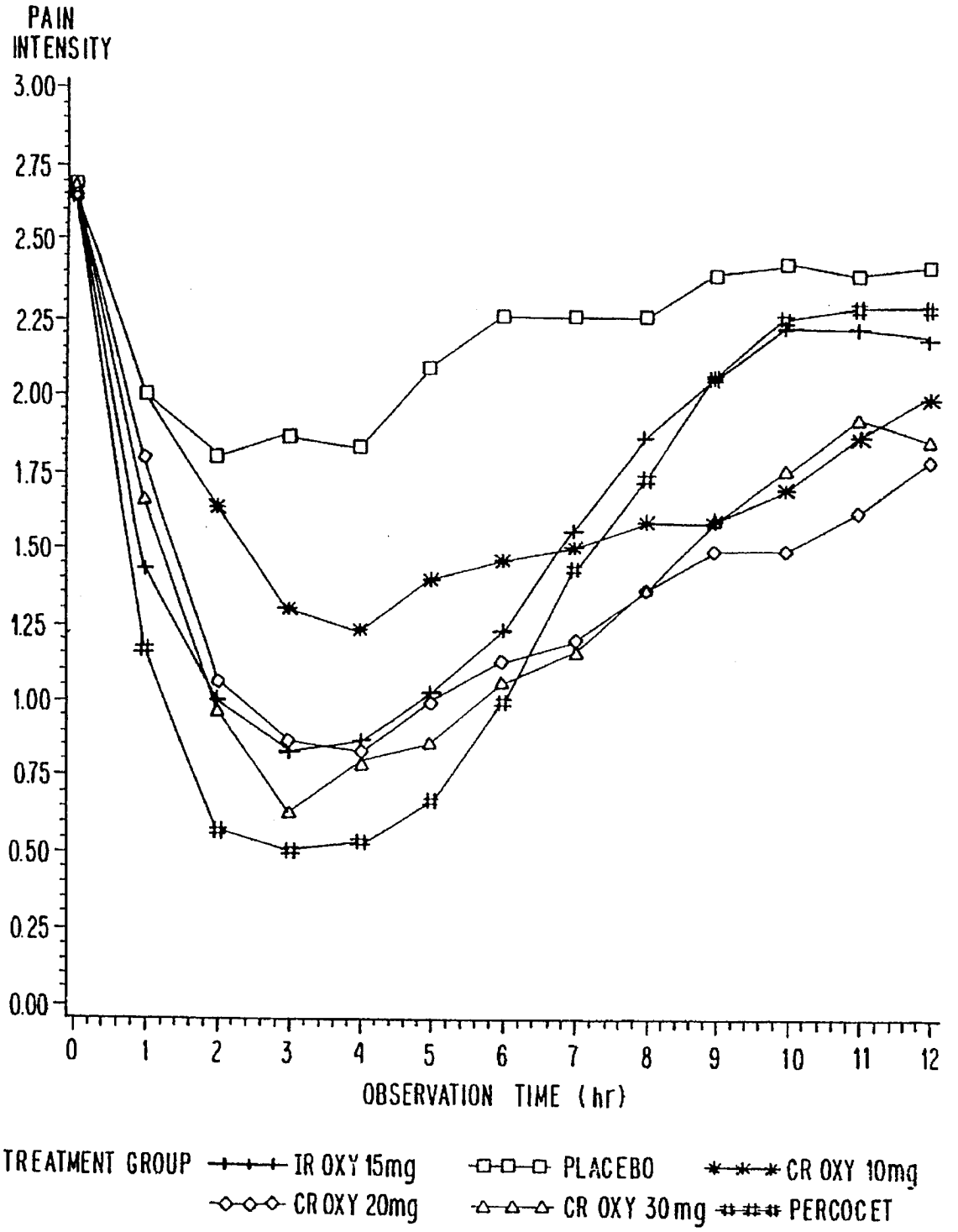

PAIN INTENSITY
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 1

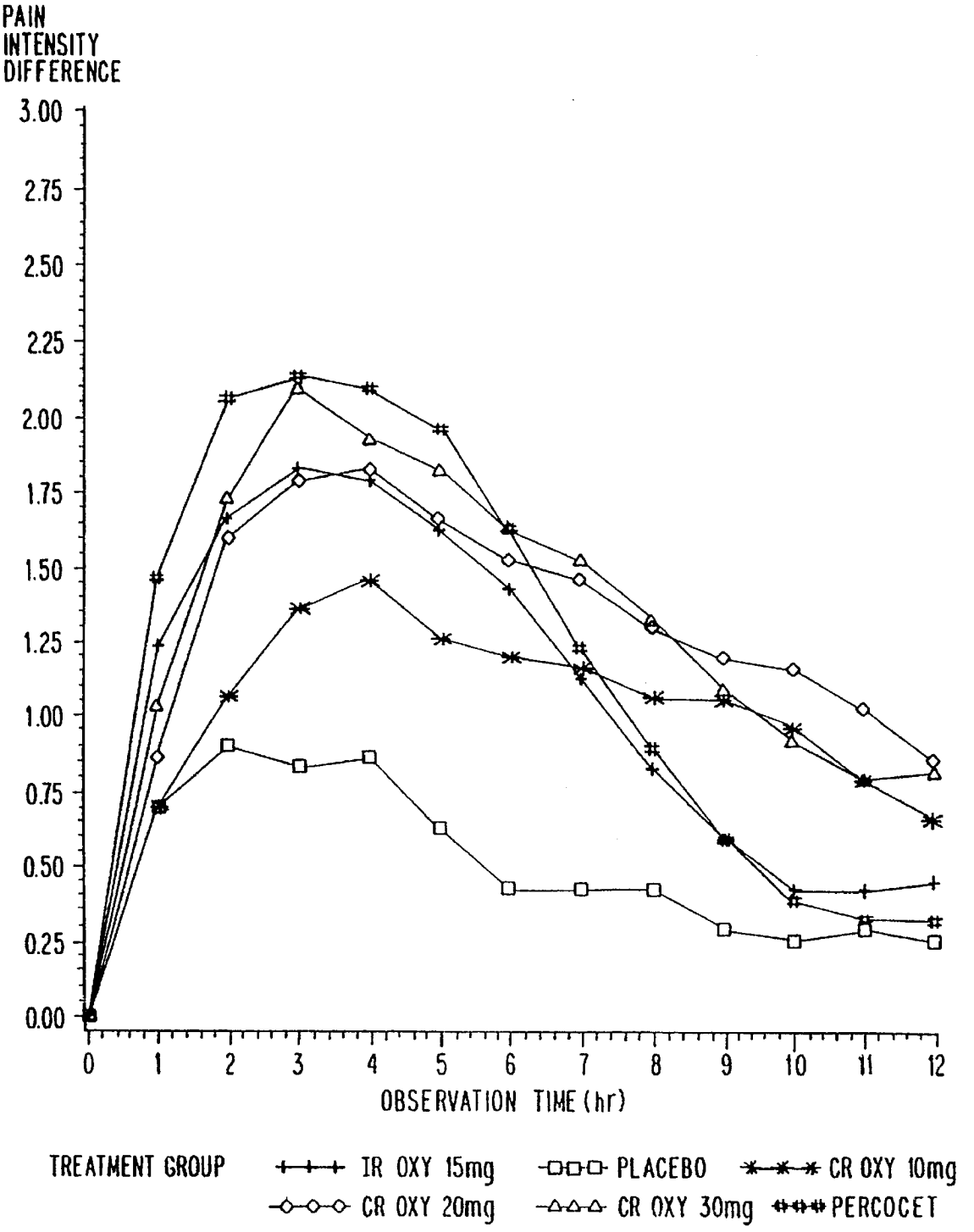

PAIN
INTENSITY
DIFFERENCE
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG.2

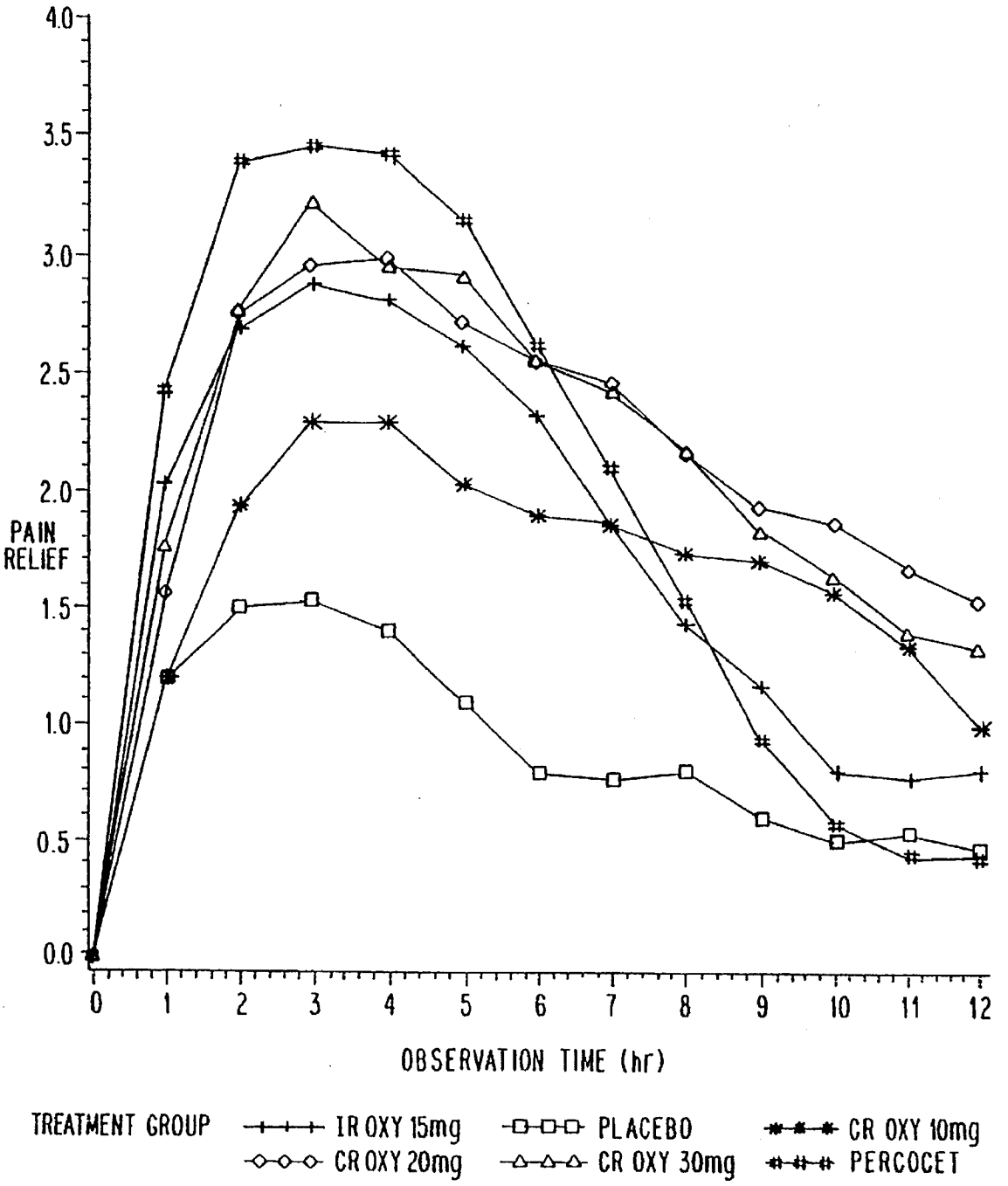

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PAIN RELIEF
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 3

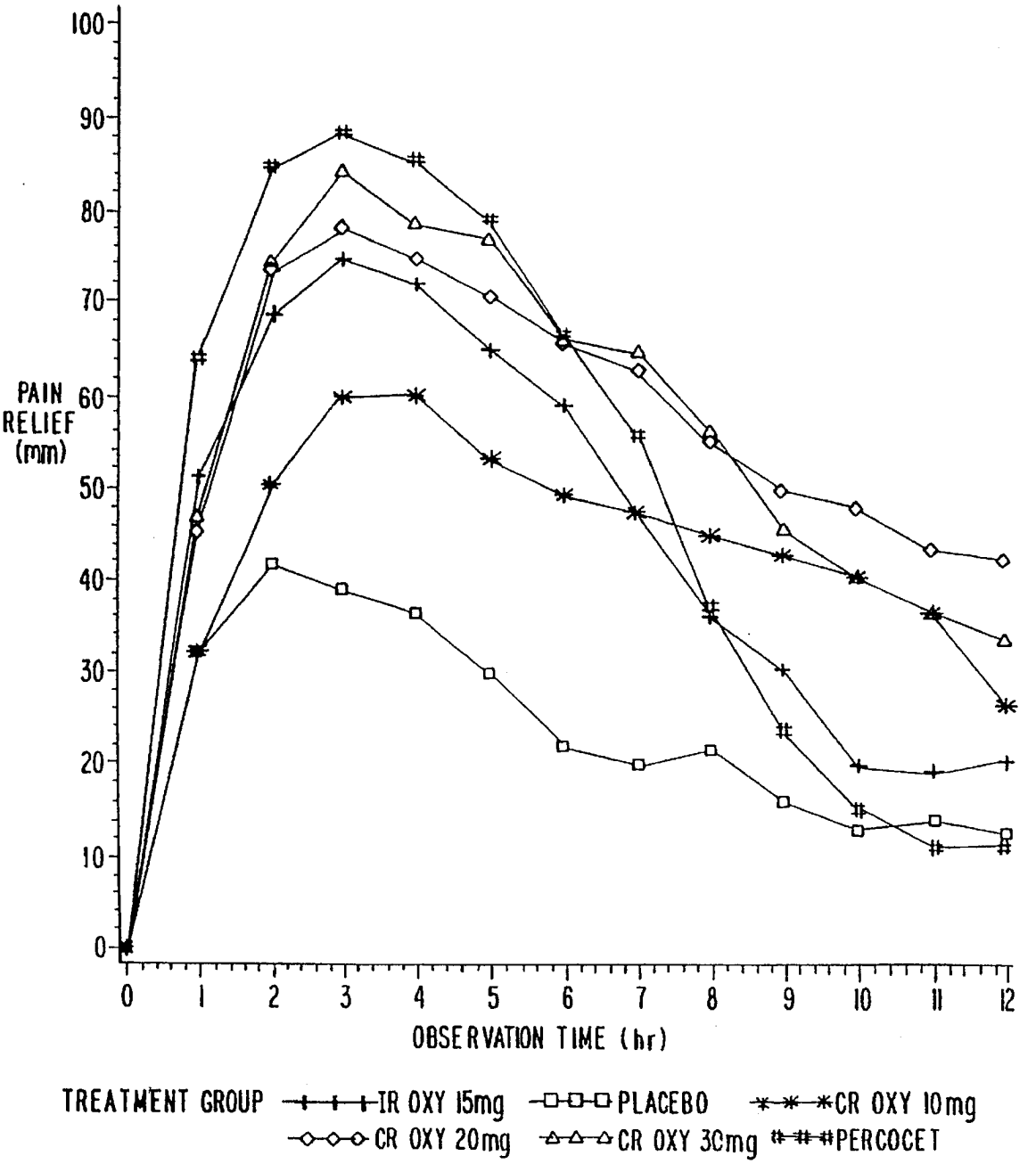

PAIN RELIEF (mm)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 4

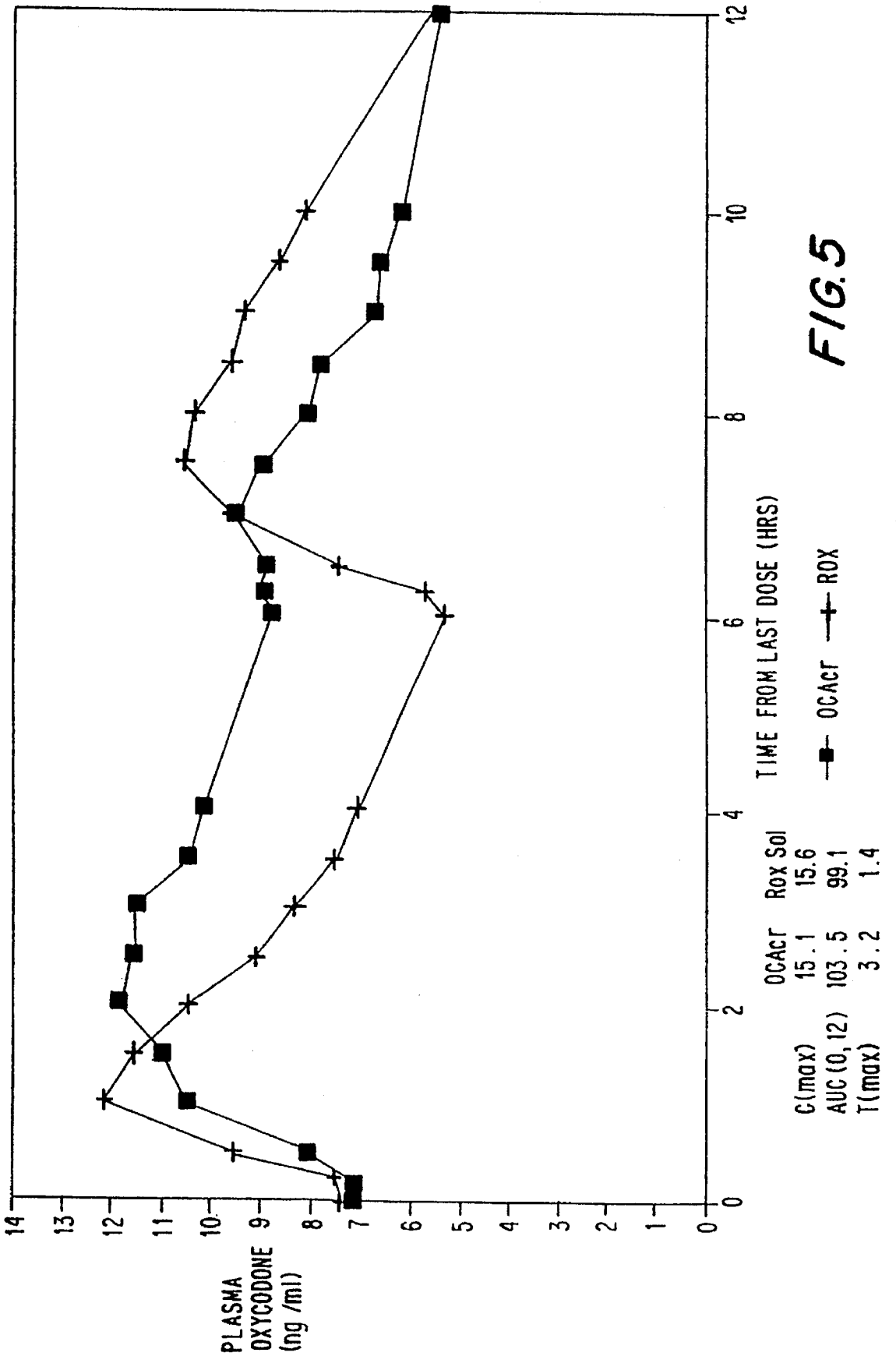

PLASMA OXYCODONE (ng/ml)
TIME FROM LAST DOSE (HRS)
OCAcr
ROX
C(max) 15.1 15.6
AUC(0,12) 103.5 99.1
T(max) 3.2 1.4
Rox Sol

FIG.5

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

This application is a continuation of Ser. No. 08/081,302, filed Jun. 18, 1993, now U.S. Pat. No. 5,549,912, which is a continuation-in-part of Ser. No. 07/800,549, filed Nov. 27, 1991, now U.S. Pat. No. 5,266,331.

BACKGROUND OF THE INVENTION

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined. The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions . . . . This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain . . . . Give each analgesic an adequate trial by dose titration . . . before switching to another drug."

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

It has previously been known in the art that controlled release compositions of opioid analgesics such as morphine, hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Pat. No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for substantially improving the efficiency and quality of pain management.

It is another object of the present invention to provide an opioid analgesic formulation which substantially improves the efficiency and quality of pain management.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the approximately eight-fold range in daily dosages required to control pain in approximately 90% of patients.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the variability in daily dosages and formulation requirements necessary to control pain in substantially all patients.

It is yet another object of the present invention to provide a method for substantially reducing the time and resources need to titrate patients requiring pain relief on opioid analgesics.

It is yet another object of the present invention to provide controlled release opioid formulations which have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects.

The above objects and others are attained by virtue of the present invention, which is related to a solid controlled release oral dosage form, the dosage form comprising from about 10 to about 40 mg of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH, such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4.5 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "substantially independent of pH" means that the difference, at any given time, between the amount of oxycodone released at, e.g., pH 1.6, and the amount released at any other pH, e.g., pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer), is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 to about 40 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising up to about 160 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIGS. **1–4** are graphs showing the time-effect curves for pain intensity differences and pain relief for Example 17;

FIG. **5** is a graph showing the mean plasma oxycodone concentration for a 10 mg controlled release oxycodone formulation prepared in accordance with the present invention and a study reference standard.

DETAILED DESCRIPTION

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

The use of from about 10 mg to about 40 mg of 12-hourly doses of controlled-release oxycodone to control pain in approximately 90% of patients relative to a wider dosage range of other μ-agonist analgesics, indicated for moderate to severe pain, is an example of the unique characteristics of the present invention. It should also be appreciated that the remaining 10% of patients would also be successfully managed with 12-hourly controlled-release oxycodone over a relatively narrower dosage range than with the use of other similar analgesics. Substantially all of those remaining 10% of patients not managed with controlled release oxycodone, 10 mg to 40 mg every 12 hours, would be managed using dosages of greater than 40 mg every 12 hours through 160 mg every 12 hours utilizing any one of a number or multiples of formulation strengths such as 10, 20, 40, 80 and 160 mg unit dosages or combinations thereof. In contrast, the use of other similar analgesics such as morphine would require a wider range of dosages to manage the remaining 10% of patients. For example, daily dosages of oral morphine equivalents in the range of 1 gram to more than 20 grams have been observed. Similarly, wide dosage ranges of oral hydromorphone would also be required.

Morphine, which is considered to be the prototypic opioid analgesic, has been formulated into a 12 hour controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Pharma, L.P.). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately ½ the dosage range as compared to commercially available controlled release morphine formulations (such as MS Contin®) to control 90% of patients with significant pain.

Repeated dose studies with the controlled release oxycodone formulations administered every 12 hours in comparison with immediate release oral oxycodone administered every 6 hours at the same total daily dose result in comparable extent of absorption, as well as comparable maximum and minimum concentrations. The time of maximum concentration occurs at approximately 2–4.5 hours after oral administration with the controlled-release product as compared to approximately 1 hour with the immediate release product. Similar repeated dose studies with MS Contin® tablets as compared to immediate release morphine provide for comparable relative results as with the controlled release oxycodone formulations of the present invention.

There exists no substantial deviation from parallelism of the dose-response curves for oxycodone either in the forms of the controlled release oxycodone formulations of the present invention, immediate release oral oxycodone or parenteral oxycodone in comparison with oral and parenteral opioids with which oxycodone has been compared in terms of dose-response studies and relative analgesic potency assays. Beaver, et al., "Analgesic Studies of Codeine and Oxycodone in Patients with Cancer. II. Comparisons of Intramuscular Oxycodone with Intramuscular Morphine and Codeine", J. Pharmacol. and Exp. Ther., Vol. 207, No. 1, pp. 101–108, reported comparable dose-response slopes for parenteral oxycodone as compared to parenteral morphine and comparable dose-response slopes for oral as compared to parenteral oxycodone.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mμ-agonist analgesic to another regardless of the dosage of the former. Unless the dose-response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

It is further clinically significant that a dose of about 80 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately 95% of patients with moderate to severe

pain, and that about 160 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately all patients with moderate to severe pain.

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4–8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2–4.5 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of up to 2 hours after administration.

A further advantage of the present composition, which releases oxycodone at a rate that is substantially independent of pH, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 500 mg, most especially between 10 and 160 mg, of oxycodone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, 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 polymer.

(b) 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. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these 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.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

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, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. 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 oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15% (by wt) of the at least one hydroxyalkyl cellulose.

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 oxycodone 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 preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit® RS PM, commercially available from Rohm Pharma.

In the present preferred dosage form, 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 considerable extent, the release rate of the oxycodone from the formulation. A ratio 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, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

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

In addition to the above ingredients, a controlled 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.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70% and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising 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 hydroxy propyl 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.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating oxycodone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}–C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

(a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronising agent,

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets—Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit® RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1

Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	% (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	213.75	57
Eudragit ® RS PM	45.0	12
Purified Water	q.s*	—
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37° C., 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5
4	58.2
8	73.2
12	81.8

TABLE 2-continued

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets—Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30° C.; and then passed through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30° C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 (10 mg controlled release oxycodone) is set forth in Table 3 below:

TABLE 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets

Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit ® RS PM	15.00	12
Ethanol	q.s.*	—
Purified Water	q.s.*	—
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric (pH 1.2) then changed to ml at pH 7.5. The results are set forth in Table 4 below:

TABLE 4

Dissolution of Oxycodone 10 mg Controlled Release Tablets

Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLES 3–4

Controlled Release Oxycodone 10 and 20 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70° C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

TABLE 5

Formula of Controlled Release Oxycodone 10 mg Tablets

Component	Mg/Tablet	% (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit ® RS 30D (solids)	10.0*	8.0
Triacetin ®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit ® RS 30D Aqueous dispersion is equivalent to 10 mg of Eudragit ® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 6 below:

TABLE 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

The formula for the tablets of Example 4 is set forth in Table 7 below:

TABLE 7

Formula of Controlled Release Oxycodone 20 mg Tablets

Component	Mg/Tablet
Oxycodone Hydrochloride	20.0
Lactose (spray dried)	59.25
Povidone	5.0
Eudragit ® RS 30D (solids)	10.0*
Triacetin ®	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total:	125.0

The tablets of Example 4 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 8 below:

TABLE 8

Dissolution of Oxycodone 20 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	31
2	44
4	57
8	71
12	79
18	86
24	89

EXAMPLES 5–6

In Example 5, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 6, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 5 and 6 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 9 and 10 below:

TABLE 9

Example 5
Percentage Oxycodone HCl 30 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

TABLE 10

Example 6
Percentage Oxycodone HCl - 10 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 7–12

In Examples 7–12, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,990,341.

In Example 7, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 8 is prepared in the same manner as Example 7; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 7 and 8 are set forth in Tables 11 and 12, respectively.

TABLE 11

Formulation of Example 7

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 12

Formulation of Example 8

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 9, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Pat. No. 4,990,341. The method of manufacture is the same as set forth in Examples 7 and 8 above. Example 10 is prepared according to Example 9, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 9 and 10 are set forth in Tables 13 and 14, respectively.

TABLE 13

Formulation of Example 9

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 14

Formulation of Example 14

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 11, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. Pat. No. 4,990,341.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C. and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 12 is prepared in identical fashion to Example 11, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 11 and 12 are set forth in Tables 15 and 16, respectively.

TABLE 15

Formulation of Example 11

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

TABLE 16

Formulation of Example 12

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 7–12 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 17.

TABLE 17

DISSOLUTION STUDIES OF EXAMPLES 7–12

Time	% Oxycodone Dissolved					
(hrs)	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 13–16

Clinical Studies

In Examples 13–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 13, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 14, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 15, a single dose study was conducted on 22 subjects using oxycodone tablets prepared according to Example 3, and compared to a 20 mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3×10 mg oxycodone tablets prepared according to Example 3, and compared to a 30 mg oxycodone immediate release solution.

The results of Examples 13–16 are set forth in Table 18.

TABLE 18

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
13	10 mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
14	5 mg IR q6h	121	17	1.2
	10 mg CR ql2h	130	17	3.2
15	20 mg IR	188	40	1.4
	2 × 10 mg CR	197	18	2.6
16	30 mg IR	306	53	1.2
	3 × 10 mg CR	350	35	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

EXAMPLE 17

Clinical Studies

In Example 17, a single dose, double blind, randomized study determined the relative analgesic efficacy, the acceptability, and relative duration of action of an oral administration of controlled release oxycodone 10, 20 and 30 mg prepared according to the present invention (CR OXY) compared to immediate release oxycodone 15 mg (IR OXY), immediate release oxycodone 10 mg in combination with acetaminophen 650 mg (IR OXY/APAP) and placebo in 180 patients with moderate or severe pain following abdominal or gynecological surgery. Patients rated their pain intensity and pain relief hourly for up to 12 hours postdosing. Treatments were compared using standard scales for pain intensity and relief, and onset and duration of pain relief.

All active treatments were significantly superior to placebo for many of the hourly measures, and for sum pain intensity differences (SPID) and total pain relief (TOTPAR). A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak pain intensity difference (PID), with CR OXY 20 mg and 30 mg being significantly better than the 10 mg dose. IR OXY was significantly superior to CR OXY 10 mg at hr 1 and 2. IR OXY/APAP was significantly superior to the 3 doses of CR OXY at hr 1, and to CR OXY 10 mg at hrs 2 through 5. Onset time was significantly shorter for the IR OXY and IR OXY/APAP treatment groups in comparison to the 3 CR OXY treatments. The distribution functions for duration of relief revealed significantly longer duration of relief for the three CR OXY doses than for IR OXY and IR OXY/APAP. No serious adverse experiences were reported. The results are more particularly reported in Table 19 below.

TABLE 19

	PATIENT DISPOSITION TREATMENT GROUP						
	IR OXY		CR OXY				
	15 mg	PLA-CEBO	10 mg	20 mg	30 mg	2 PERC*	TOTAL
Enrolled and Randomized to Study Treatment	31	31	30	30	30	30	182
Entered the Study Treatment Phase	31	31	30	30	30	30	182

TABLE 19-continued

	PATIENT DISPOSITION TREATMENT GROUP						
	IR OXY		CR OXY				
	15 mg	PLA-CEBO	10 mg	20 mg	30 mg	2 PERC*	TOTAL
Completed the Study	31	30	30	30	30	30	181
Discontinued from the Study	0	1	0	0	0	0	1
Excluded from Efficacy Analysis							
Vomited prior to 1 hr post dose	0	1	0	0	0	0	1
Inadvertently received rescue during study	1	0	0	0	0	0	1
Analysis Population:							
Evaluable for Safety and Efficacy	30	30	30	30	30	30	180
Evaluable for Safety	31	31	30	30	30	30	182

*2 tablets of Percocet ®

The time-effect curves for pain intensity, pain intensity differences and pain relief are shown in FIGS. **1–4.** CR OXY 10 mg had significantly ($p<0.05$) lower pain intensity scores than the placebo-treated patients at hours 3–11 and lower pain scores than IR OXY 15 mg and Percocet® at hour 10. CR OXY 20 mg has significantly ($p<0.05$) lower pain intensity scores compared to placebo at hours 2–11 and significantly ($p<0.05$) lower pain scores than CR OXY 10 mg, IR OXY 15 mg and Percocet at hours 9–11. CR OXY 30 mg had significantly ($p<0.05$) lower pain scores than placebo at hours 2–11 and lower pain scores than CR OXY 10 mg at hours 2, 3, and 5 and lower scores than Percocet® at hour 10.

For hourly pain relief scores categorical and visual analog scales (CAT and VAS), CR OXY 10 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 3–11 and higher relief scores than IR OXY and Percocet® at hour 10 (and Percocet® at hour 11). CR OXY 20 mg had significantly ($p<0.05$) higher relief scores than placebo at hours 2–12 and higher relief scores than Percocet® at hours 9–12. In addition, CR OXY had significantly ($p<0.05$) higher pain relief than IR OXY at hours 10–12. CR OXY 30 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 2–12 and higher scores than Percocet® at hours 9–12 and IR OXY 15 mg at hour 10.

Each treatment group was significantly ($p<0.05$) better than placebo with respect to the sum of the pain intensity differences (SPID) and total pain relief (TOTPAR).

Duration of pain relief as measured by the patient stopwatch method showed that CR OXY 10 mg, 20 mg and 30 mg had significantly ($p<0.05$) longer duration of action compared to IR OXY 15 mg and 2 tablets Percocet®. In addition, the three controlled-release formulations had significantly ($p<0.05$) longer times to remedication compared to Percocet®.

Before remedication, a total of 104 (57%) of patients reported 120 adverse experiences. The most common were somnolence, fever, dizziness and headache.

Based upon the results of this study it is concluded that the controlled release oxycodone formulations of the present invention relieve moderate to severe post-operative pain, e.g., due to abdominal or gynecological surgery in women. There is a dose response noted in which placebo<10 mg<20 mg<30 mg CR OXY following a single dose. Onset of action occurred in one hour with peak effects noted from 2 to 5 hours and a duration of effect from 10 to 12 hours. In the chronic pain situation steady state dosing may prolong this effect. Side effects are expected and easily managed. Headache may be related to dose. Dizziness and somnolence were reported.

IR OXY 15 mg has an intermediate peak effect compared to controlled release oxycodone. Its duration of action is shorter (6–8 hours). Percocet® is quite effective in terms of onset, peak effect and safety. The duration of action is 6–8 hours.

In summary, CR OXY was clearly an effective oral analgesic, with a slower onset but a longer duration of effect than either IR OXY or IR OXY/APAP.

EXAMPLE 18

Clinical Studies

In Example 18, a steady state crossover trial was conducted in 21 normal male subjects comparing

a. CR OXY 10 mg administered every 12 hours (q12h); and

b. Roxicodone® oral solution 5 mg (ROX) administered every 6 hours (q6h),

Treatment (b) was the study reference standard. The average age was 34 years, height 176 cm and weight 75 kg. No unusual features were noted about the group.

FIG. 5 shows the mean plasma oxycodone concentrations for the two formulations over the 12 hour dosing interval. The results are summarized in Table 18 in terms of mean values, ratios of mean values and 90% confidence intervals.

As inspection of Table 18 reveals, with one exception, no significant differences were detected between the two formulations. The single exception is the mean t_{max} for CR OXY of 3.18 hours which, as expected for a controlled release formulation, significantly exceeded the ROX mean of 1.38 hours. Mean AUC-based bioavailability, (ROX= 100%) was 104.4% with 90% confidence limits of 90.9 to 117.9%. Thus, the FDA specification of ±20% is met so that the study results support an assertion of equal oxycodone availability.

TABLE 20

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q12H) AND ROXIDODONE ® ORAL SOLUTION (5 mg q6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ROXI (%)	90% CI*
C_{max} (ng/mL)				
ARITH. MEAN(SD)	15.11 (4.69)	15.57 (4.41)	97.08	85.59–108.50
GEOMETRIC MEAN	14.43	15.01	95.14	
C_{min} (ng/mL)				
ARITH. MEAN(SD)	6.24 (2.64)	6.47 (3.07)	96.41	80.15–112.74
GEOMETRIC MEAN	5.62	5.83	96.48	
t_{max} (hrs)				

TABLE 20-continued

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q12H) AND ROXIDODONE ® ORAL SOLUTION (5 mg q6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ROXI (%)	90% CI*
ARITH. MEAN(SD) AUC(0–12 hrs)	3.18 (2.21)	1.38 (0.71)*	230.17	160.71–298.71
ARITH. MEAN(SD)	103.50 (40.03)	99.10 (35.04)	104.44	90.92–117.94
GEOMETRIC MEAN	97.06	93.97	103.29	
% Swing				
ARITH. MEAN(SD)	176.36 (139.0)	179.0 (124.25)	98.53	62.06–134.92
% Fluctuation				
ARITH. MEAN(SD)	108.69 (38.77)	117.75 (52.47)	92.22	76.81–107.57
End Point				
ARITH. MEAN(SD)	–1.86 (2.78)	–1.86 (2.19)	99.97	117.77–22.23

*90% Confidence Interval
Significant Difference $p < 0.05$

EXAMPLE 19

Clinical Studies

In Example 19, twenty-four normal, healthy male subjects were enrolled in a randomized single-dose two-way crossover study to compare the plasma oxycodone concentrations obtained after dosing with two controlled-release oxycodone 10 mg tablets versus 20 mg (20 ml of 5 mg/5 ml) of immediate release (IR) oxycodone hydrochloride solution. Twenty-three subjects completed the study and were eligible for analysis.

Plasma oxycodone concentrations were determined by a high performance liquid chromatographic procedure. Arithmetic Mean C_{max}, t_{max}, AUC, and half-lives calculated from individual plasma oxycodone concentration-versus-time data are set forth in Table 21:

TABLE 21

Pharmacokinetic Parameter	Reference Product IR Oxycodone 20 mg	Test Product CR Oxycodone 2 × 10 mg F. ° (%)		90% Confidence Interval
C_{max} (ng/ml)	41.60	18.62	44.75	32.5–57.0
t_{max} (hours)	1.30	2.62	200.83	169.8–232.6
AUC (0–36) (mg × hr/ml)	194.35	199.62	102.71	89.5–115.9
AUC (0–∞) (ng × hr/ml)	194.38	208.93	107.49	92.9–121.9
$t_{½ (elim)}$ (hrs)	3.21	7.98*	249.15	219.0–278.8
$t_{½ (abs)}$ (hrs)	0.35	0.92*	264.17	216.0–310.7

F ° (%) = Oral bioavailability (CR oxycodone 2 × 10 mg/IR oxycodone 20 mg)
*Statistically significant ($p = 0.0001$)

For C_{max}, t_{max}, $t_{1/2}$(elim) and $t_{1/2}$(abs) there were statistically significant differences between the CR OXY and IR

OXY. There were no statistically significant differences between the two treatments in the extent of absorption [AUC (0,36), AUC (0,∞)]. The 90% confidence interval for CR OXY relative to IR OXY relative was 89.5%–115.9% for AUC (0,36) and 92.9%–121.9% for AUC (0,∞). Based on the 90% confidence interval analysis, the controlled-release oxycodone tablets were equivalent in extent of absorption (AUC 0,36) to the immediate-release oxycodone solution. The controlled-release oxycodone absorption was slower by approximately 1.3 hours. No statistically significant differences were noted between the two treatments with reference to adverse experiences, none of which were considered clinically unusual for opiates for this type of study.

The above studies demonstrate a significant dose-response relationship utilizing the controlled release oxycodone formulations of the present invention at dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Kaiko R. S., Van Wagoner D., Brown J., et al., "Controlled-Release Oral Morphine (MS Contin® Tablets, MSC) in Postoperative Pain.", Pain Suppl., 5:S149 1990, who compared 30, 60, 90, and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield, et al., "Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations", Clinical Pharmacology & Therapeutics, (in press), who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone, based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 120 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

2. The controlled release oxycodone formulation of claim **1**, comprising from about 10 to about 40 mg oxycodone based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration.

3. The controlled release oxycodone formulation of claim **1**, comprising from about 40 mg to about 160 mg oxycodone based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 60 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration.

4. The solid controlled release oxycodone formulation of claim **1**, comprising

oxycodone hydrochloride dispersed in an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing, and a suitable amount of a suitable pharmaceutical diluent.

5. The solid controlled release oxycodone formulation of claim **1**, comprising:

(a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronising agent or an acrylic polymer or copolymer, such that the total dosage of oxycodone in said dosage form is from about 10 to about 160 mg based on the hydrochloride salt; and

(b) a film coating on said spheroids which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form.

6. The controlled release oxycodone formulation of claim **1**, comprising a tablet wherein said oxycodone is dispersed in a controlled release matrix.

7. The controlled release oxycodone formulation of claim **1**, wherein said oxycodone is in the form of the hydrochloride salt.

8. A method for substantially reducing the range in daily dosages required to control pain in human patients, comprising administering to a human patient an oral controlled release dosage formulation comprising from about 10 to about 160 mg oxycodone or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone form about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 120 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

9. A method for substantially reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering to a human patient an oral solid controlled release dosage formulation comprising from about 10 mg to about 40 mg oxycodone or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of up to about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 30 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

10. A method for substantially reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering to a human patient an oral solid controlled release dosage formulation comprising from about 40 mg to about 160 mg oxycodone or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone from about 60 to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 30 to about 120 ng/ml from about 10 to about 14 hours after administration after repeated dosing every 12 hours through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

* * * * *

EXHIBIT C

US005549912A

United States Patent [19]

Oshlack et al.

[11] **Patent Number: 5,549,912**

[45] **Date of Patent: *Aug. 27, 1996**

[54] **CONTROLLED RELEASE OXYCODONE COMPOSITIONS**

[75] Inventors: **Benjamin Oshlack**, New York, N.Y.; **Mark Chasin**, Manalpan, N.J.; **John J. Minogue**, Mount Vernon, N.Y.; **Robert F. Kaiko**, Weston, Conn.

[73] Assignee: **Euro-Celtique, S.A.**, Luxembourg, Luxembourg

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,266,331.

[21] Appl. No.: **81,302**

[22] PCT Filed: **Nov. 25, 1992**

[86] PCT No.: **PCT/US92/10146**

§ 371 Date: **Jun. 18, 1993**

§ 102(e) Date: **Jun. 18, 1993**

[87] PCT Pub. No.: **WO93/10765**

PCT Pub. Date: **Jun. 10, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 800,549, Nov. 27, 1991, Pat. No. 5,266,331.

[51] **Int. Cl.**[6] **A61K 9/22**; A61K 9/26

[52] **U.S. Cl.** **424/468**; 424/469; 424/470; 424/486; 424/487; 424/488; 424/494; 424/496; 424/497; 424/498; 424/501; 424/502; 424/495

[58] **Field of Search** 424/486, 468–470, 424/487–88, 494, 496–498, 464–469

[56] **References Cited**

U.S. PATENT DOCUMENTS

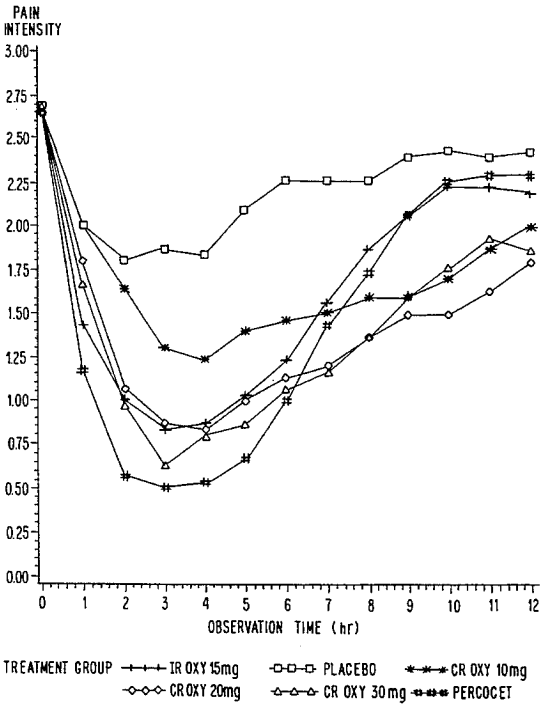
4,861,598	8/1989	Oshlack	424/470
4,990,341	2/1991	Goldie et al.	424/484

Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients by administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, such that a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions are achieved. Controlled release oxycodone formulations for achieving the above are also disclosed.

9 Claims, 5 Drawing Sheets



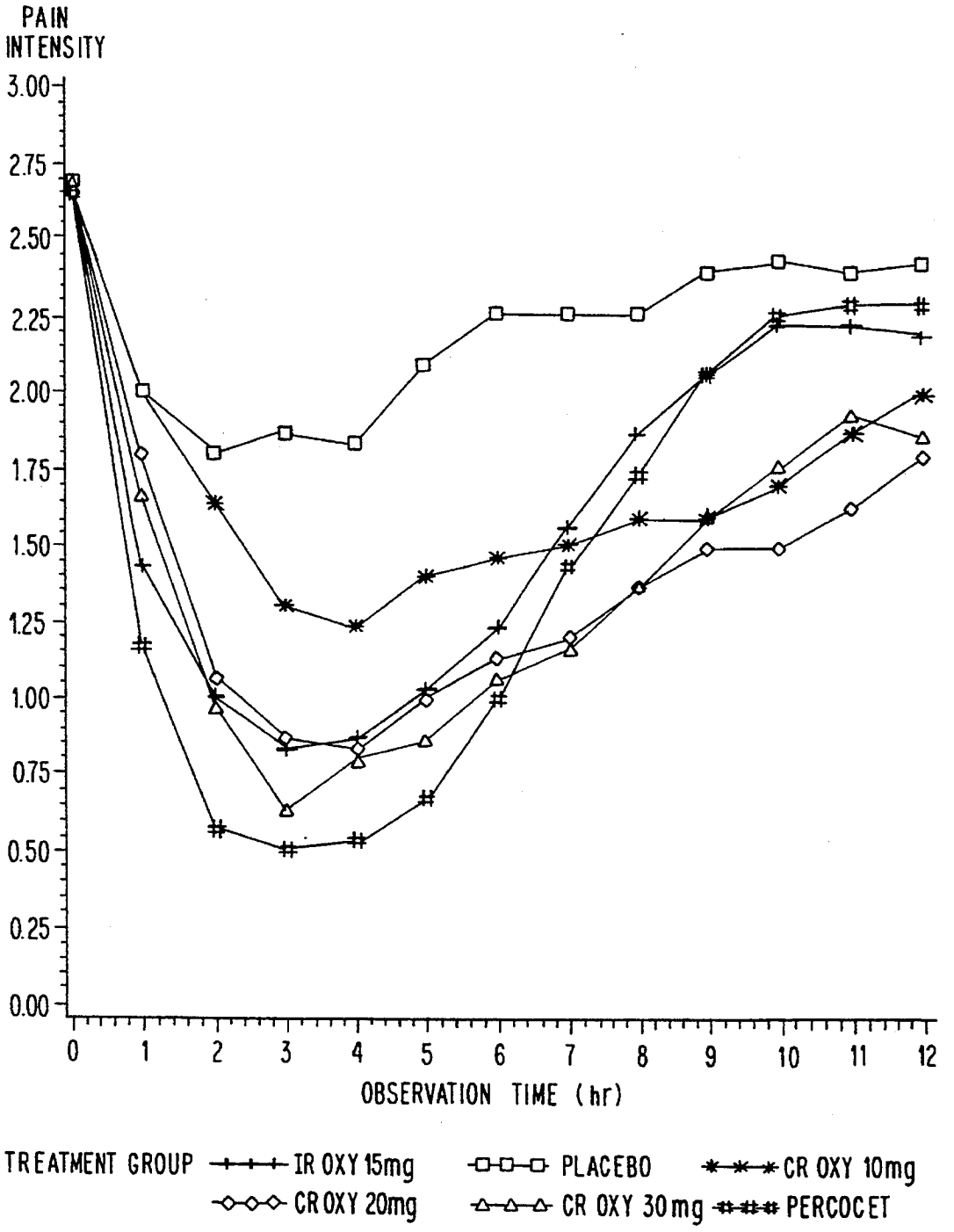

PAIN INTENSITY
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 1

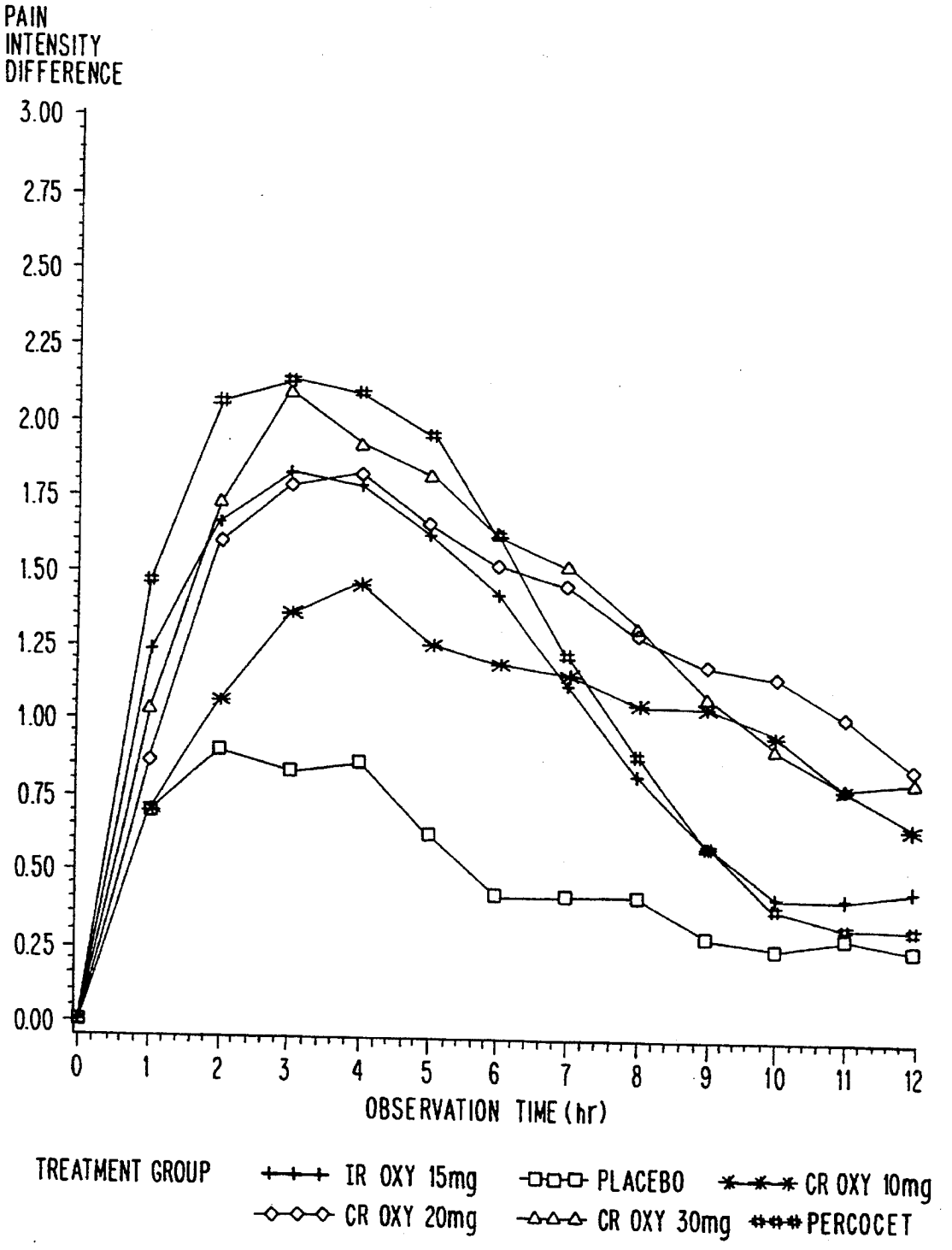

PAIN
INTENSITY
DIFFERENCE
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG.2

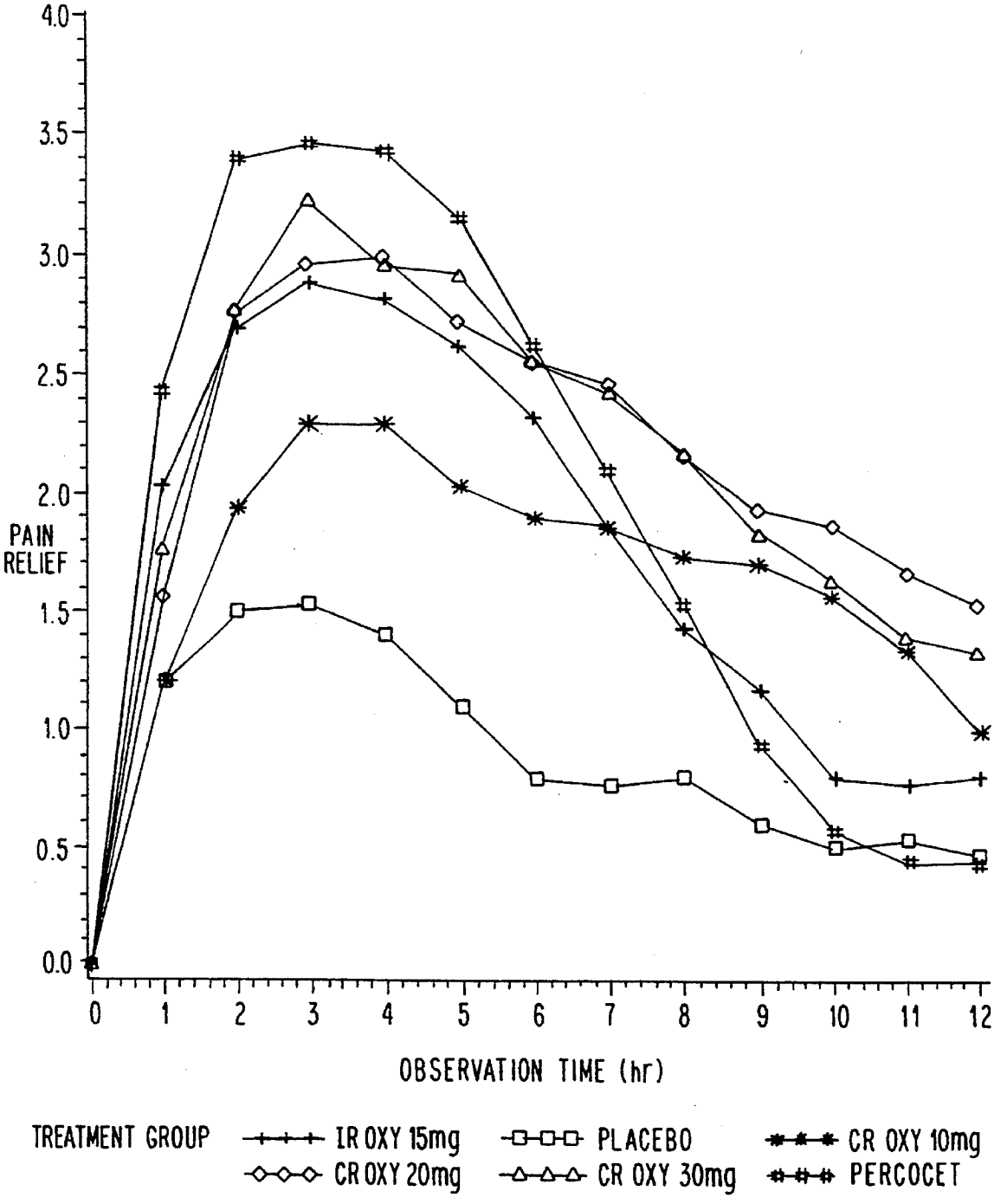

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PAIN RELIEF
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 3

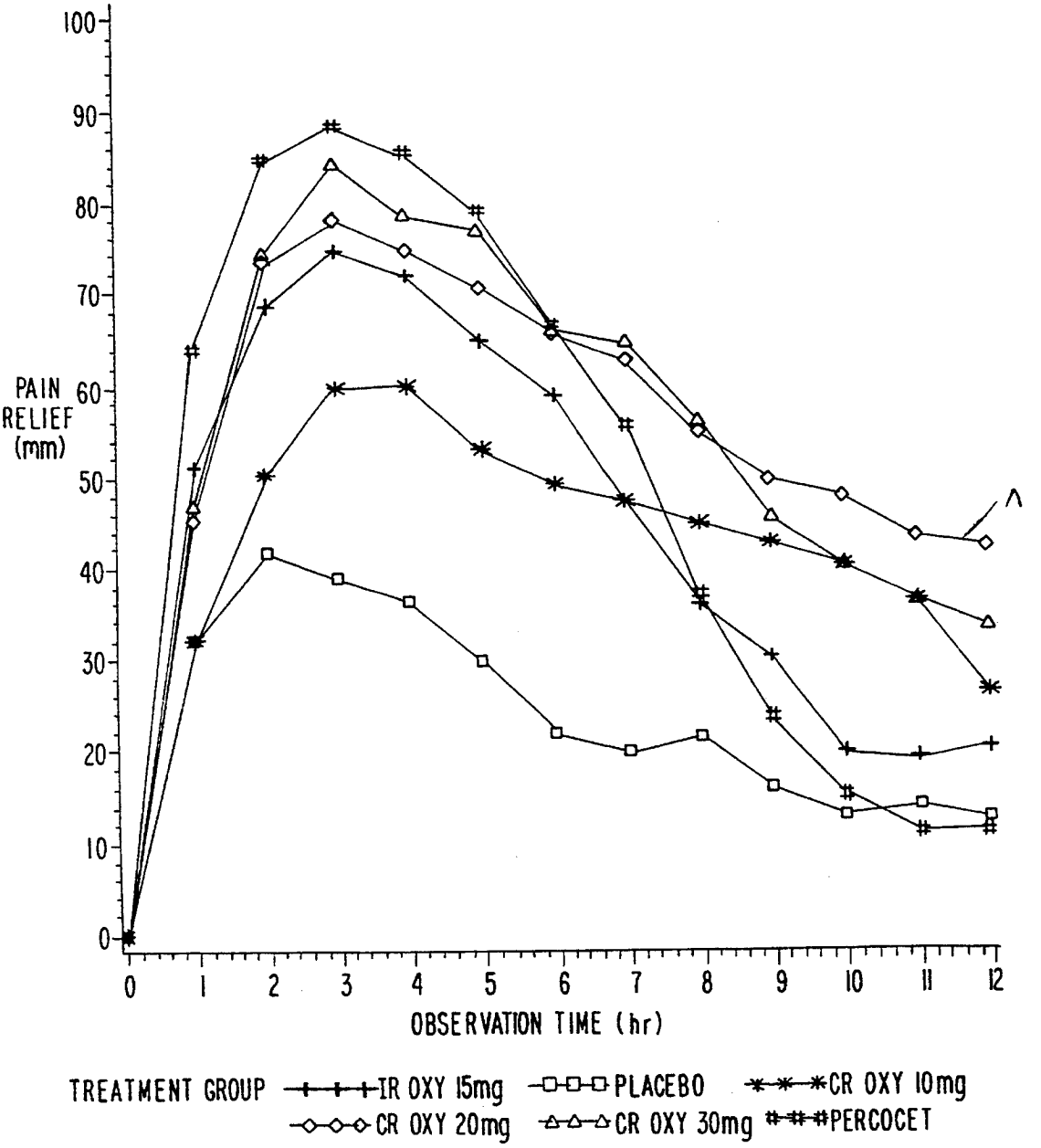

100
90
80
70
60
50
40
30
20
10
0
PAIN RELIEF (mm)
0 1 2 3 4 5 6 7 8 9 10 11 12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 4

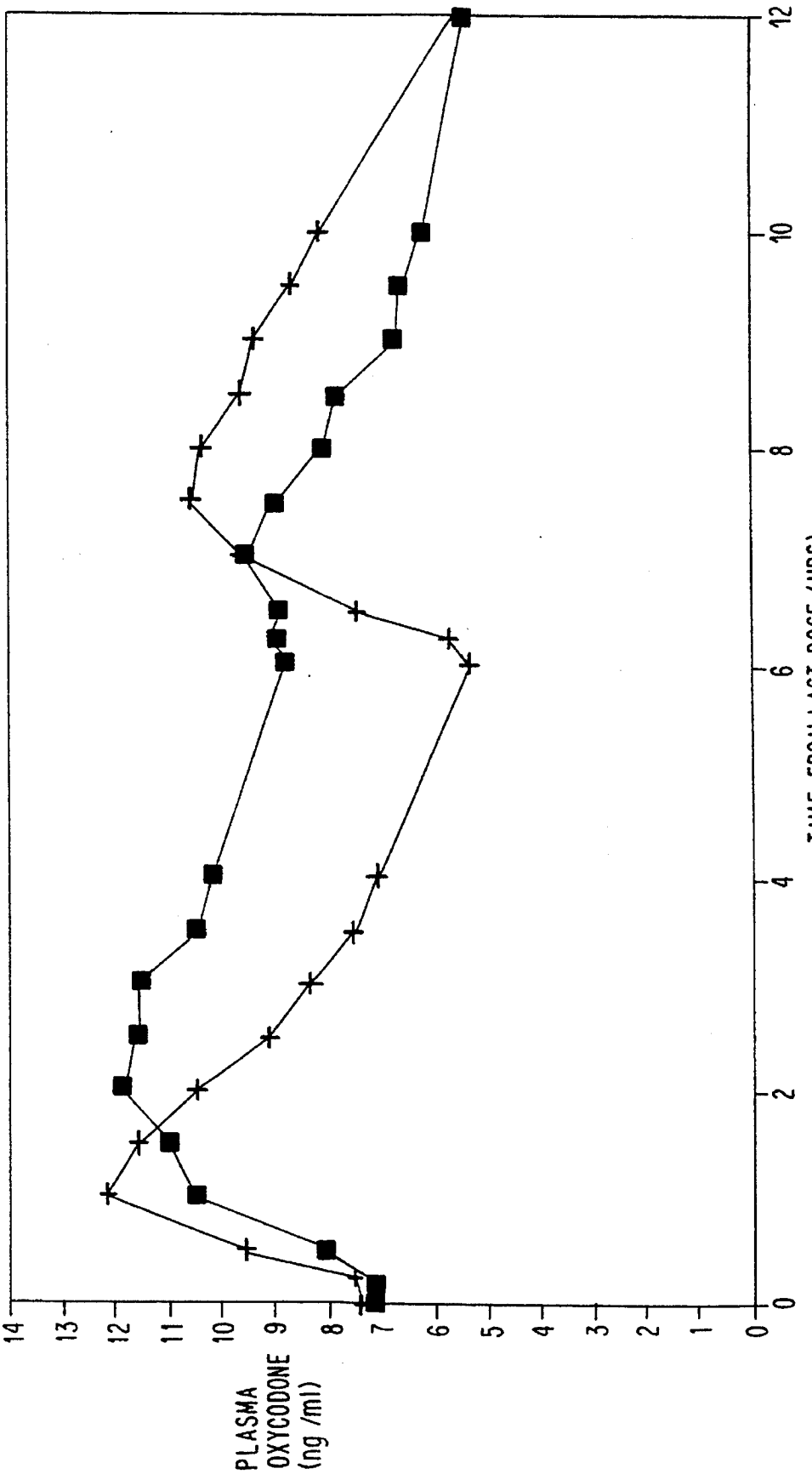

PLASMA OXYCODONE (ng /ml)
TIME FROM LAST DOSE (HRS)
OCAcr
ROX
C(max) 15.1 15.6
AUC(0,12) 103.5 99.1
T(max) 3.2 1.4
Rox Sol

FIG.5

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 07/800,549, filed Nov. 27, 1991, now U.S. Pat. No. 5,266,331.

BACKGROUND OF THE INVENTION

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined. The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions . . . . This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain . . . . Give each analgesic an adequate trial by dose titration . . . before switching to another drug."

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

It has previously been known in the art that controlled release compositions of opioid analgesics such as morphine, hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Pat. No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for substantially improving the efficiency and quality of pain management.

It is another object of the present invention to provide an opioid analgesic formulation which substantially improves the efficiency and quality of pain management.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the approximately eight-fold range in daily dosages required to control pain in approximately 90% of patients.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the variability in daily dosages and formulation requirements necessary to control pain in substantially all patients.

It is yet another object of the present invention to provide a method for substantially reducing the time and resources need to titrate patients requiring pain relief on opioid analgesics.

It is yet another object of the present invention to provide controlled release opioid formulations which have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects.

The above objects and others are attained by virtue of the present invention, which is related to a solid controlled release oral dosage form, the dosage form comprising from about 10 to about 40 mg of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH, such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4.5 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "substantially independent of pH" means that the difference, at any given time, between the amount of oxycodone released at, e.g., pH 1.6, and the amount released at any other pH, e.g., pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer), is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 to about 40 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising up to about 160 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIGS. **1–4** are graphs showing the time-effect curves for pain intensity differences and pain relief for Example 17;

FIG. **5** is a graph showing the mean plasma oxycodone concentration for a 10 mg controlled release oxycodone formulation prepared in accordance with the present invention and a study reference standard.

DETAILED DESCRIPTION

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

The use of from about 10 mg to about 40 mg of 12-hourly doses of controlled-release oxycodone to control pain in approximately 90% of patients relative to a wider dosage range of other mμ-agonist analgesics, indicated for moderate to severe pain, is an example of the unique characteristics of the present invention. It should also be appreciated that the remaining 10% of patients would also be successfully managed with 12-hourly controlled-release oxycodone over a relatively narrower dosage range than with the use of other similar analgesics. Substantially all of those remaining 10% of patients not managed with controlled release oxycodone, 10 mg to 40 mg every 12 hours, would be managed using dosages of greater than 40 mg every 12 hours through 160 mg every 12 hours utilizing any one of a number or multiples of formulation strengths such as 10, 20, 40, 80 and 160 mg unit dosages or combinations thereof. In contrast, the use of other similar analgesics such as morphine would require a wider range of dosages to manage the remaining 10% of patients. For example, daily dosages of oral morphine equivalents in the range of 1 gram to more than 20 grams have been observed. Similarly, wide dosage ranges of oral hydromorphone would also be required.

Morphine, which is considered to be the prototypic opioid analgesic, has been formulated into a 12 hour controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Pharma, L.P.). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately ½ the dosage range as compared to commercially available controlled release morphine formulations (such as MS Contin®) to control 90% of patients with significant pain.

Repeated dose studies with the controlled release oxycodone formulations administered every 12 hours in comparison with immediate release oral oxycodone administered every 6 hours at the same total daily dose result in comparable extent of absorption, as well as comparable maximum and minimum concentrations. The time of maximum concentration occurs at approximately 2–4.5 hours after oral administration with the controlled-release product as compared to approximately 1 hour with the immediate release product. Similar repeated dose studies with MS Contin® tablets as compared to immediate release morphine provide for comparable relative results as with the controlled release oxycodone formulations of the present invention.

There exists no substantial deviation from parallelism of the dose-response curves for oxycodone either in the forms of the controlled release oxycodone formulations of the present invention, immediate release oral oxycodone or parenteral oxycodone in comparison with oral and parenteral opioids with which oxycodone has been compared in terms of dose-response studies and relative analgesic potency assays. Beaver, et al., "Analgesic Studies of Codeine and Oxycodone in Patients with Cancer. II. Comparisons of Intramuscular Oxycodone with Intramuscular Morphine and Codeine", J. Pharmacol. and Exp. Ther., Vol. 207, No. 1, pp. 101–108, reported comparable dose-response slopes for parenteral oxycodone as compared to parenteral morphine and comparable dose-response slopes for oral as compared to parenteral oxycodone.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mμ-agonist analgesic to another regardless of the dosage of the former. Unless the dose-response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

It is further clinically significant that a dose of about 80 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately 95% of patients with moderate to severe

pain, and that about 160 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately all patients with moderate to severe pain.

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4–8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2–4.5 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of up to 2 hours after administration.

A further advantage of the present composition, which releases oxycodone at a rate that is substantially independent of pH, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 500 mg, most especially between 10 and 160 mg, of oxycodone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, 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 polymer.

(b) 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. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these 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.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

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, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. 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 oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15% (by wt) of the at least one hydroxyalkyl cellulose.

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 oxycodone 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 preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit® RS PM, commercially available from Rohm Pharma.

In the present preferred dosage form, 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 considerable extent, the release rate of the oxycodone from the formulation. A ratio 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, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

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

In addition to the above ingredients, a controlled 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.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70% and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising 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 hydroxy propyl 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.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating hydromorphone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}–C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

(a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronising agent,

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets—Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit® RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1

Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	% (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	213.75	57
Eudragit ® RS PM	45.0	12
Purified Water	q.s*	—
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37° C., 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5
4	58.2

TABLE 2-continued

Dissolution of Oxycodone 30 mg Controlled Release Tablets	
Time	% Oxycodone Dissolved
8	73.2
12	81.8
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets—Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30° C.; and then passed through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30° C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 (10 mg controlled release oxycodone) is set forth in Table 3 below:

TABLE 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets		
Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit ® RS PM	15.00	12
Ethanol	q.s.*	—
Purified Water	q.s.*	—
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric (pH 1.2) then changed to 900 ml at pH 7.5.

The results are set forth in Table 4 below:

TABLE 4

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLES 3–4

Controlled Release Oxycodone 10 and 20 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70° C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

TABLE 5

Formula of Controlled Release Oxycodone 10 mg Tablets		
Component	Mg/Tablet	% (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit ® RS 30D (solids)	10.0*	8.0
Triacetin ®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit ® RS 30D Aqueous dispersion is equivalent to 10 mg of Eudragit ® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 6 below:

TABLE 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

The formula for the tablets of Example 4 is set forth in Table 7 below:

TABLE 7

Formula of Controlled Release Oxycodone 20 mg Tablets

Component	Mg/Tablet
Oxycodone Hydrochloride	20.0
Lactose (spray dried)	59.25
Povidone	5.0
Eudragit ® RS 30D (solids)	10.0*
Triacetin ®	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total:	125.0

The tablets of Example 4 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 8 below:

TABLE 8

Dissolution of Oxycodone 20 mg Controlled Release Tablets

Hour	% Oxycodone Dissolved
1	31
2	44
4	57
8	71
12	79
18	86
24	89

EXAMPLES 5–6

In Example 5, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 6, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 5 and 6 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 9 and 10 below:

TABLE 9

Example 5
Percentage Oxycodone HCl
30 mg Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

TABLE 10

Example 6
Percentage Oxycodone HCl - 10 mg
Tablets Dissolved Over Time

pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 7–12

In Examples 7–12, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,990,341.

In Example 7, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 8 is prepared in the same manner as Example 7; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 7 and 8 are set forth in Tables 11 and 12, respectively.

TABLE 11

Formulation of Example 7

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 12

Formulation of Example 8

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 9, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Pat. No. 4,990,341. The method of manufacture is the same as set forth in Examples 7 and 8 above. Example 10 is prepared according to Example 9, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 9 and 10 are set forth in Tables 13 and 14, respectively.

TABLE 13

Formulation of Example 9

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 14

Formulation of Example 14

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 11, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. Pat. No. 4,990,341.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C. and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 12 is prepared in identical fashion to Example 11, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 11 and 12 are set forth in Tables 15 and 16, respectively.

TABLE 15

Formulation of Example 11

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

TABLE 16

Formulation of Example 12

Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 7–12 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 17.

TABLE 17

DISSOLUTION STUDIES OF EXAMPLES 7–12

Time	% Oxycodone Dissolved					
(hrs)	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 13–16

Clinical Studies

In Examples 13–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 13, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 14, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 15, a single dose study was conducted on subjects using oxycodone tablets prepared according to Example 3, and compared to a 20 mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3×10 mg oxycodone tablets prepared according to Example 3, and compared to a 30 mg oxycodone immediate release solution.

The results of Examples 13–16 are set forth in Table 18.

TABLE 18

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
13	10 mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
14	5 mg IR q6h	121	17	1.2
	10 mg CR q12h	130	17	3.2
15	20 mg IR	188	40	1.4
	2 × 10 mg CR	197	18	2.6
16	30 mg IR	306	53	1.2
	3 × 10 mg CR	350	35	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

EXAMPLE 17

Clinical Studies

In Example 17, a single dose, double blind, randomized study determined the relative analgesic efficacy, the acceptability, and relative duration of action of an oral administration of controlled release oxycodone 10, 20 and 30 mg prepared according to the present invention (CR OXY) compared to immediate release oxycodone 15 mg (IR OXY), immediate release oxycodone 10 mg in combination with acetaminophen 650 mg (IR OXY/APAP) and placebo in 180 patients with moderate or severe pain following abdominal or gynecological surgery. Patients rated their pain intensity and pain relief hourly for up to 12 hours postdosing. Treatments were compared using standard scales for pain intensity and relief, and onset and duration of pain relief.

All active treatments were significantly superior to placebo for many of the hourly measures, and for sum pain intensity differences (SPID) and total pain relief (TOTPAR). A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak pain intensity difference (PID), with CR OXY 20 mg and 30 mg being significantly better than the 10 mg dose. IR OXY was significantly superior to CR OXY 10 mg at hr 1 and 2. IR OXY/APAP was significantly superior to the 3 doses of CR OXY at hr 1, and to CR OXY 10 mg at hrs 2 through 5. Onset time was significantly shorter for the IR OXY and IR OXY/APAP treatment groups in comparison to the 3 CR OXY treatments. The distribution functions for duration of relief revealed significantly longer duration of relief for the three CR OXY doses than for IR OXY and IR OXY/APAP. No serious adverse experiences were reported. The results are more particularly reported in Table 19 below.

TABLE 19

	PATIENT DISPOSITION TREATMENT GROUP						
	IR OXY		CR OXY				
	15 mg	PLACEBO	10 mg	20 mg	30 mg	2 PERC*	TOTAL
Enrolled and Randomized to Study Treatment	31	31	30	30	30	30	182
Entered the Study Treatment Phase	31	31	30	30	30	30	182
Completed the Study	31	30	30	30	30	30	181
Discontinued from the Study	0	1	0	0	0	0	1
Excluded from Efficacy Analysis Vomited prior to 1 hr post dose	0	1	0	0	0	0	1
Inadvertently received rescue during study	1	0	0	0	0	0	1
Analysis Population: Evaluable for Safety and Efficacy	30	30	30	30	30	30	180
Evaluable for Safety	31	31	30	30	30	30	182

*2 tablets of Percocet ®

The time-effect curves for pain intensity, pain intensity differences and pain relief are shown in FIGS. **1–4**. CR OXY 10 mg had significantly ($p<0.05$) lower pain intensity scores than the placebo-treated patients at hours 3–11 and lower pain scores than IR OXY 15 mg and Percocet® at hour 10. CR OXY 20 mg has significantly ($p<0.05$) lower pain

intensity scores compared to placebo at hours 2–11 and significantly ($p<0.05$) lower pain scores than CR OXY 10 mg, IR OXY 15 mg and Percocet at hours 9–11. CR OXY 30 mg had significantly ($p<0.05$) lower pain scores than placebo at hours 2–11 and lower pain scores than CR OXY 10 mg at hours 2, 3, and 5 and lower scores than Percocet® at hour 10.

For hourly pain relief scores categorical and visual analog scales (CAT and VAS), CR OXY 10 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 3–11 and higher relief scores than. IR OXY and Percocet® at hour 10 (and Percocet® at hour 11). CR OXY 20 mg had significantly ($p<0.05$) higher relief scores than placebo at hours 2–12 and higher relief scores than Percocet® at hours 9–12. In addition, CR OXY had significantly ($p<0.05$) higher pain relief than IR OXY at hours 10–12. CR OXY 30 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 2–12 and higher scores than Percocet® at hours 9–12 and IR OXY 15 mg at hour 10.

Each treatment group was significantly ($p<0.05$) better than placebo with respect to the sum of the pain intensity differences (SPID) and total pain relief (TOTPAR).

Duration of pain relief as measured by the patient stopwatch method showed that CR OXY 10 mg, 20 mg and 30 mg had significantly ($p<0.05$) longer duration of action compared to IR OXY 15 mg and 2 tablets Percocet®. In addition, the three controlled-release formulations had significantly ($p<0.05$) longer times to remedication compared to Percocet®.

Before remedication, a total of 104 (57%) of patients reported 120 adverse experiences. The most common were somnolence, fever, dizziness and headache.

Based upon the results of this study it is concluded that the controlled release oxycodone formulations of the present invention relieve moderate to severe postoperative pain, e.g., due to abdominal or gynecological surgery in women. There is a dose response noted in which placebo<10 mg<20 mg<30 mg CR OXY following a single dose. Onset of action occurred in one hour with peak effects noted from 2 to 5 hours and a duration of effect from 10 to 12 hours. In the chronic pain situation steady state dosing may prolong this effect. Side effects are expected and easily managed. Headache may be related to dose. Dizziness and somnolence were reported.

IR OXY 15 mg has an intermediate peak effect compared to controlled release oxycodone. Its duration of action is shorter (6–8 hours). Percocet® is quite effective in terms of onset, peak effect and safety. The duration of action is 6–8 hours.

In summary, CR OXY was clearly an effective oral analgesic, with a slower onset but a longer duration of effect than either IR OXY or IR OXY/APAP.

EXAMPLE 18

Clinical Studies

In Example 18, a steady state crossover trial was conducted in 21 normal male subjects comparing

a. CR OXY 10 mg administered every 12 hours (q12h); and

b. Roxicodone® oral solution 5 mg (ROX) administered every 6 hours (q6h),

Treatment (b) was the study reference standard. The average age was 34 years, height 176 cm and weight 75 kg. No unusual features were noted about the group.

FIG. **5** shows the mean plasma oxycodone concentrations for the two formulations over the 12 hour dosing interval. The results are summarized in Table 18 in terms of mean values, ratios of mean values and 90% confidence intervals.

As inspection of Table 18 reveals, with one exception, no significant differences were detected between the two formulations. The single exception is the mean t_{max} for CR OXY of 3.18 hours which, as expected for a controlled release formulation, significantly exceeded the ROX mean of 1.38 hours. Mean AUC-based bioavailability, (ROX= 100%) was 104.4% with 90% confidence limits of 90.9 to 117.9%. Thus, the FDA specification of ±20% is met so that the study results support an assertion of equal oxycodone availability.

TABLE 20

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q 12H) AND ROXICODONE ® ORAL SOLUTION (5 mg q 6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
C_{max} (ng/mL)				
ARITH. MEAN (SD)	15.11(4.69)	15.57(4.41)	97.08	85.59–108.50
GEOMETRIC MEAN	14.43	15.01	95.14	
C_{min} (ng/mL)				
ARITH. MEAN (SD)	6.24(2.64)	6.47(3.07)	96.41	80.15–112.74
GEOMETRIC MEAN	5.62	5.83	96.48	
t_{max} (hrs)	3.18(2.21)	1.38(0.71)*	230.17	160.71–298.71
ARITH. MEAN (SD)				
AUC (0–12 hrs)				
ARITH. MEAN (SD)	103.50(40.03)	99.10(35.04)	104.44	90.92–117.94
GEOMETRIC MEAN	97.06	93.997	103.29	
% Swing	176.36(139.0)	179.0(124.25)	98.53	62.06–134.92
ARITH. MEAN				

TABLE 20-continued

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q 12H) AND ROXICODONE ® ORAL SOLUTION (5 mg q 6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
(SD) % Fluctuation ARITH. MEAN (SD)	108.69(38.77)	117.75(52.47)	92.22	76.81–107.57
End Point ARITH. MEAN (SD)	−1.86(2.78)	−1.86(2.19)	99.97	117.77–22.23

*90% Confidence Interval
--Signicant Difference $p < 0.05$

EXAMPLE 19

Clinical Studies

In Example 19, twenty-four normal, healthy male subjects were enrolled in a randomized single-dose two-way cross-over study to compare the plasma oxycodone concentrations obtained after dosing with two controlled-release oxycodone 10 mg tablets versus 20 mg (20 ml of 5 mg/5 ml) of immediate release (IR) oxycodone hydrochloride solution. Twenty-three subjects completed the study and were eligible for analysis.

Plasma oxycodone concentrations were determined by a high performance liquid chromatographic procedure. Arithmetic Mean C_{max}, t_{max}, AUC, and half-lives calculated from individual plasma oxycodone concentration-versus-time data are set forth in Table 21:

TABLE 21

Pharmacokinetic Parameter	Reference Product IR Oxycodone 20 mg	Test Product CR Oxycodone 2 × 10 mg F. (%)		90% Confidence Interval
C_{max} (ng/ml)	41.60	18.62	44.75	32.5–57.0
t_{max} (hours)	1.30	2.62	200.83	169.8–232.6
AUC (0–36) (mg × hr/ml)	194.35	199.62	102.71	89.5–115.9
AUC (0–∞) (ng × hr/ml)	194.38	208.93	107.49	92.9–121.9
$t_{½(elim)}$ (hrs)	3.21	7.98*	249.15	219.0–278.8
$t_{½(abs)}$ (hrs)	0.35	0.92*	264.17	216.0–310.7

F. % = Oral bioavailability (CR oxycodone 2 × 10 mg/IR oxycodone 20 mg)
*Statistically significant ($p = 0.0001$)

For C_{max}, t_{max}, $t_{1/2}$(elim)and $t_{1/2}$(abs)there were statistically significant differences between the CR OXY and IR OXY. There were no statistically significant differences between the two treatments in the extent of absorption [AUC (0,36), AUC (0,∞). The 90% confidence interval for CR OXY relative to IR OXY relative was 89.5%–115.9% for AUC (0,36) and 92.9%–121.9% for AUC (0,∞). Based on the 90% confidence interval analysis, the controlled-release oxycodone tablets were equivalent in extent of absorption (AUC 0,36) to the immediate-release oxycodone solution. The controlled-release oxycodone absorption was slower by approximately 1.3 hours. No statistically significant differences were noted between the two treatments with reference to adverse experiences, none of which were considered clinically unusual for opiates for this type of study.

The above studies demonstrate a significant dose-response relationship utilizing the controlled release oxycodone formulations of the present invention at dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Kaiko R. S., Van Wagoner D., Brown J., et al., "Controlled-Release Oral Morphine (MS Contin® Tablets MSC) in Postoperative Pain", Pain Suppl., 5:S149 1990, who compared 30, 60, 90, and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield, et al., "Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations", Clinical Pharmacology & Therapeutics, (in press), who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

2. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

3. A solid controlled release oral dosage form, comprising

(a) oxycodone or a salt thereof in an amount from about 10 to about 160 mg;

(b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

4. The controlled release composition of claim **3**, wherein said controlled release matrix comprises an acrylic resin.

5. A solid controlled release oral dosage form, comprising

(a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronising agent or an acrylic polymer or copolymer, such that the total dosage of oxycodone in said dosage form is from about 10 to about 160 mg;

(b) a film coating which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form;

said composition providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

6. The controlled release composition of claim **5**, wherein said film coating comprises a water insoluble material selected from the group consisting of shellac or zein, a water insoluble cellulose, or a polymethacrylate.

7. A controlled release tablet for oral administration comprising from about 10 to about 160 mg oxycodone or an oxycodone salt dispersed in a controlled release matrix, said tablet providing an in-vitro dissolution of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH and chosen such that a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml is obtained in vivo from a mean of about 2 to about 4.5 hours after administration of the dosage form, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

8. A dosage form according to claim **7**, wherein the in vitro dissolution rate is between 17.5% and 38% (by wt) oxycodone released after 1 hour, between 30% and 50% (by wt) oxycodone released after 2 hours, between 50% and 70% (by wt) oxycodone released after 4 hours and between 60% and 80% (by wt) oxycodone released after 6 hours.

9. A dosage form according to claim **7**, wherein the in vitro dissolution rate is between 17.5% and 32.5% (by wt) oxycodone released after 1 hour, between 35% and 45% (by wt) oxycodone released after 2 hours, between 55% and 65% (by wt) oxycodone released after 4 hours and between 65% and 75% (by wt) oxycodone released after 6 hours.

* * * * *

JS 44 (Rev. 3/99)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
PURDUE PHARMA L.P.,
THE P.F. LABORATORIES, INC. and
PURDUE PHARMACEUTICALS L.P.

DEFENDANTS
KV PHARMACEUTICAL COMPANY and
ACTAVIS TOTOWA LLC

(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF _____
(EXCEPT IN U.S. PLAINTIFF CASES)

COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

(c) ATTORNEYS (FIRM ADDRESS AND TELEPHONE NUMBER)
Jack B. Blumenfeld, Esquire
Morris, Nichols, Arsht & Tunnell LLP
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347

ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN "X" IN ONE BOX ONLY)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN "X" IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated or Principal Place of Business in This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated and Principal Place of Business in Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(PLACE AN "X" IN ONE BOX ONLY)*

CONTRACT
- ☐ **110** Insurance
- ☐ **120** Marine
- ☐ **130** Miller Act
- ☐ **140** Negotiable Instrument
- ☐ **150** Recovery of Overpayment & Enforcement of Judgement
- ☐ **151** Medicare Act
- ☐ **152** Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ **153** Recovery of Overpayment of Veteran's Benefits
- ☐ **160** Stockholder Suits
- ☐ **190** Other Contract
- ☐ **195** Contract Product Liability

TORTS

PERSONAL INJURY
- ☐ **310** Airplane
- ☐ **315** Airplane Product Liability
- ☐ **320** Assault Libel & Slander
- ☐ **330** Federal Employers Liability
- ☐ **340** Marine
- ☐ **345** Marine Product Liability
- ☐ **350** Motor Vehicle
- ☐ **355** Motor Vehicle Product Liability
- ☐ **360** Other Personal Injury

PERSONAL INJURY
- ☐ **362** Personal Injury - Med Malpractice
- ☐ **365** Personal Injury - Product Liability
- ☐ **368** Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ **370** Other Fraud
- ☐ **371** Truth in Lending
- ☐ **380** Other Personal Property Damage
- ☐ **385** Property Damage Product Liability

REAL PROPERTY
- ☐ **210** Land Condemnation
- ☐ **220** Foreclosure
- ☐ **230** Rent Lease & Ejectment
- ☐ **240** Torts to Land
- ☐ **245** Tort Product Liability
- ☐ **290** All Other Real Property

CIVIL RIGHTS
- ☐ **441** Voting
- ☐ **442** Employment
- ☐ **443** Housing/ Accommodations
- ☐ **444** Welfare
- ☐ **440** Other Civil Rights

PRISONER PETITIONS
- ☐ **510** Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ **530** General
- ☐ **535** Death Penalty
- ☐ **540** Mandamus & Other
- ☐ **550** Civil Rights
- ☐ **555** Prison Condition

FORFEITURE/PENALTY
- ☐ **610** Agriculture
- ☐ **620** Other Food & Drug
- ☐ **625** Drug Related Seizure of Property 21 USC 881
- ☐ **630** Liquor Laws
- ☐ **640** R R & Truck
- ☐ **650** Airline Regs
- ☐ **660** Occupational Safety/Health
- ☐ **690** Other

LABOR
- ☐ **710** Fair Labor Standards Act
- ☐ **720** Labor/Mgmt. Relations
- ☐ **730** Labor Mgmt. Reporting & Disclosure Act
- ☐ **740** Railway Labor Act
- ☐ **790** Other Labor Litigation
- ☐ **791** Empl Ret Inc Security Act

BANKRUPTCY
- ☐ **422** Appeal 28 USC 158
- ☐ **423** Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ **820** Copyrights
- ☒ **830** Patent
- ☐ **840** Trademark

SOCIAL SECURITY
- ☐ **861** HIA (1395ff)
- ☐ **862** Black Lung (923)
- ☐ **863** DIWC/DIWW (405(g))
- ☐ **864** SSID Title XVI
- ☐ **865** RSI (405(g))

FEDERAL TAX SUITS
- ☐ **870** Taxes (U.S. Plaintiff or Defendant
- ☐ **871** IRS - Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks or Banking
- ☐ 450 Commerce/ICC Rates/etc
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

V. ORIGIN *(PLACE AN "X" IN ONE BOX ONLY)*

☒ 1 Original Proceeding | ☐ 2 Removed From State Court | ☐ 3 Remanded From Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred From another district (specify) ____ | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgement

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE BRIEF STATEMENT OF CAUSE DO NOT CITE JURISDICTIONAL STATUTES UNLESS DIVERSITY)

Patent Infringement under 35 U.S.C. § 271.

VII. REQUESTED IN COMPLAINT
☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23
DEMAND $
CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ YES ☒ NO

VIII. RELATED CASE(S) IF ANY (See Instructions) **SEE ATTACHMENT**
JUDGE _____ DOCKET NUMBER _____

DATE
January 16, 2007

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

JS 44 Reverse (Rev. 12/96)

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS-44

Authority For Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. this form, approved by the Judicial Conference of the Untied States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. **(a) Plaintiffs – Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify the first agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE; In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a). F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS-44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C., Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

V. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section IV above, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause.

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS-44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

RELATED CASES

- *Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc., and The Purdue Pharma Company* v. *Boehringer Ingelheim GmbH, Roxane Laboratories, Inc., and Boehringer Ingelheim Corporation*, 99 Civ. 3658 (S.D.N.Y.) (SHS)
- *Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc., and The Purdue Pharma Company* v. *Endo Pharmaceuticals Inc. and Endo Pharmaceuticals Holdings Inc.*, 00 Civ. 8029, 01 Civ. 2109, and 01 Civ. 8177 (S.D.N.Y.) (SHS)
- *Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc., and The Purdue Pharma Company* v. *Teva Pharmaceuticals USA, Inc.*, 01 Civ. 8507, 01 Civ 11212, and 03 Civ 2312 (S.D.N.Y.) (SHS)
- *Purdue Pharma L.P., The Purdue Frederick Company, The P.F. Laboratories, Inc., and The Purdue Pharma Company* v. *Impax Laboratories, Inc.*, 02 Civ. 2803, 02 Civ. 7569, and 02 Civ. 8036 (S.D.N.Y.) (SHS)
- *Purdue Pharma L.P., The P.F. Laboratories, Inc., and Purdue Pharmaceuticals L.P.* v. *Mallinckrodt Inc*., 06 CV 13095 (S.D.N.Y.) (Unassigned)
- *Rite Aid Corporation* v. *Purdue Pharma L.P., The Purdue Frederick Company, Purdue Pharmaceuticals L.P., The P.F. Laboratories Inc., The Purdue Pharma Company, and Euro-Celtique, S.A.*, 06 CV 15304 (S.D.N.Y.) (Unassigned)
- *Safeway Inc.* v. *Purdue Pharma L.P., The Purdue Frederick Company, Purdue Pharmaceuticals L.P., The P.F. Laboratories Inc., The Purdue Pharma Company, and Euro-Celtique, S.A.*, 06 CV 15326 (S.D.N.Y.) (Unassigned)
- *In re: Oxycontin Antitrust Litigation*s, 04 md 1603 (S.D.N.Y.) (SHS)

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. -07-32

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 2 COPIES OF AO FORM 85.

JAN 16 2007
(Date forms issued)

John Ryan Plochary
(Signature of Party or their Representative)

John Ryan Plocharz
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action