11 CIV 7104

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

PURDUE PHARMA L.P.,
THE P.F. LABORATORIES, INC.,
PURDUE PHARMACEUTICALS L.P.,
and RHODES TECHNOLOGIES,

Plaintiffs,

v.

RANBAXY INC.,
RANBAXY PHARMACEUTICALS INC.,
and RANBAXY LABORATORIES LTD.,

Defendants.

C.A. No. _____

COMPLAINT

Plaintiffs Purdue Pharma L.P., The P.F. Laboratories, Inc., Purdue Pharmaceuticals L.P., and Rhodes Technologies 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.

THE PARTIES: PLAINTIFFS

2. 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, CT 06901-3431. Purdue Pharma is an owner of United States Patent Nos. 7,674,799, 7,674,800, and 7,683,072 identified in paragraphs 19-21 below. Purdue Pharma is also the holder of New Drug Application ("NDA") No. 022272

for the controlled-release oxycodone pain-relief medication OxyContin®, and is involved in the sales of OxyContin® in the United States.

3. 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, NJ 07512. P.F. Labs is an owner of United States Patent Nos. 7,674,799, 7,674,800, and 7,683,072 identified in paragraphs 19-21 below, and is involved in the manufacture of controlled-release oxycodone pain-relief medication under the brand name OxyContin®.

4. 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, NC 27893. Purdue Pharmaceuticals is an owner of United States Patent Nos. 7,674,799, 7,674,800, and 7,683,072 identified in paragraphs 19-21 below, and is involved in the manufacture of controlled-release oxycodone pain-relief medication under the brand name OxyContin®.

5. Plaintiff Rhodes Technologies ("Rhodes") is a general partnership organized and existing under the laws of the State of Delaware, having a place of business at 498 Washington Street, Coventry, RI 02816. Rhodes is an owner of United States Patent Nos. 7,674,799, 7,674,800, and 7,683,072 identified in paragraphs 19-21 below, and is involved in the manufacture of controlled-release oxycodone pain-relief medication under the brand name OxyContin®.

6. Plaintiffs Purdue Pharma, P.F. Labs, Purdue Pharmaceuticals, and Rhodes are associated companies.

THE PARTIES: DEFENDANTS

7. Upon information and belief, Defendant Ranbaxy Inc. ("RI") is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 600 College Road East, Suite 2100, Princeton, NJ 08540.

8. Upon information and belief, RI is registered as a Foreign Business Corporation by the New York State Department of State, Division of Corporations and lists Corporation Service Company, 80 State Street, Albany, NY 12207-2543 as its registered agent.

9. Upon information and belief, Defendant Ranbaxy Pharmaceuticals Inc. ("RPI") is a corporation organized and existing under the laws of the State of Florida, having its principal place of business at 9431 Florida Mining Boulevard East, Jacksonville, FL 32257.

10. Upon information and belief, RPI is registered as a Pharmacy Establishment in the State of New York by the New York State Department of Education, Office of the Professions. (Registration No. 025942). The Registration has an active status and is valid through February 29, 2012.

11. Upon information and belief, Defendant Ranbaxy Laboratories Ltd. ("RLL") is a corporation organized under the laws of India, having its principal place of business at Plot No. 90, Sector 32, Gurgaon – 122 001 (Haryana), India.

12. Upon information and belief, RI is a wholly owned subsidiary of RLL.

13. Upon information and belief, RPI is a wholly owned subsidiary of RLL.

14. Upon information and belief, the acts of RLL complained of herein, were done at the direction of, with the authorization of, and with the cooperation, participation, and assistance of RPI and RI.

15. RI, RPI, and RLL are referred hereinafter collectively as "Ranbaxy."

JURISDICTION AND VENUE

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

17. This Court has personal jurisdiction over Ranbaxy because, *inter alia*, Ranbaxy has purposefully availed itself of the rights and benefits of the laws of this State and this Judicial District. Upon information and belief, Ranbaxy does business in this State and this Judicial District, has engaged in continuous and systematic contact with this State and this Judicial District, and derives substantial revenue from things used or consumed in this State and this Judicial District. Upon information and belief, Ranbaxy engages in the manufacture and sale of a range of pharmaceutical products within and directed to the United States, this State, and this Judicial District specifically. Ranbaxy has previously consented to personal jurisdiction in this Judicial District in patent litigation concerning the same Abbreviated New Drug Application ("ANDA") at issue in this case directed to generic oxycodone hydrochloride extended release tablets. *See Purdue Pharma L.P. et al. v. Ranbaxy Inc.*, No. 11-civ-2401 (S.D.N.Y. Apr. 8, 2011). Further, this Court has personal jurisdiction over Ranbaxy because RPI is registered as a Pharmacy Establishment in the State of New York by the New York State Department of Education, Office of the Professions. This Court also has personal jurisdiction over Ranbaxy because RI is registered as a Foreign Business Corporation by the New York State Department of State, Division of Corporations. In addition, upon information and belief, Ranbaxy is actively preparing to make the proposed generic copies of OxyContin® that are the subject of ANDA No. 202427, and to use, sell and offer for sale such generic copies in this State and this Judicial District.

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

THE PATENTS IN SUIT

19. Plaintiffs Purdue Pharma, P.F. Labs, Purdue Pharmaceuticals, and Rhodes are the lawful owners of all right, title and interest in United States Patent No. 7,674,799 entitled "OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE" ("the '799 patent"), including all right to sue and to recover for past infringement thereof, which patent is listed in FDA's Orange Book as covering the drug OxyContin®, which is the subject of approved NDA No. 022272. A copy of the '799 patent is attached hereto as Exhibit A, which was duly and legally issued on March 9, 2010, naming Robert Chapman, Lonn S. Rider, Qi Hong, Donald Kyle, and Robert Kupper as the inventors.

20. Plaintiffs Purdue Pharma, P.F. Labs, Purdue Pharmaceuticals, and Rhodes are the lawful owners of all right, title and interest in United States Patent No. 7,674,800 entitled "OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE" ("the '800 patent"), including all right to sue and to recover for past infringement thereof, which patent is listed in the FDA's Orange Book as covering the drug OxyContin®, which is the subject of approved NDA No. 022272. A copy of the '800 patent is attached hereto as Exhibit B, which was duly and legally issued on March 9, 2010, naming Robert Chapman, Lonn S. Rider, Qi Hong, Donald Kyle, and Robert Kupper as the inventors.

21. Plaintiffs Purdue Pharma, P.F. Labs, Purdue Pharmaceuticals, and Rhodes are the lawful owners of all right, title and interest in United States Patent No. 7,683,072 entitled "OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE" ("the '072 patent"), including all right to sue and to recover for past infringement thereof, which patent is listed in the FDA's Orange Book as covering the drug OxyContin®, which is the subject of approved NDA No. 022272. A copy of the '072 patent is

attached hereto as Exhibit C, which was duly and legally issued on March 23, 2010, naming Robert Chapman, Lonn S. Rider, Qi Hong, Donald Kyle, and Robert Kupper as the inventors.

DEFENDANTS' ANDA

22. Upon information and belief, Ranbaxy submitted ANDA No. 202427 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, sale, offer for sale or importation of generic oxycodone hydrochloride extended release tablets, 10 mg, 15 mg, and 20 mg, ("proposed generic copies of OxyContin®") based on the Reference Listed Drug ("RLD") OxyContin®, which is the subject of approved NDA No. 022272, before the expiration of the '799, '800, and '072 patents.

23. Upon information and belief, Ranbaxy's ANDA No. 202427 contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that "no valid, enforceable claim" of the '799, '800, and '072 patents listed in the FDA's Orange Book as covering the drug OxyContin®, which is the subject of approved NDA No. 022272, "will be infringed by the manufacture, importation, use, sale, or offer for sale" of its proposed generic copies of OxyContin®.

24. In letters dated August 25, 2011 addressed to Plaintiff Purdue Pharma, The University of Texas System, and Grünenthal GmbH, and received by Plaintiff Purdue Pharma on August 25, 2011, Ranbaxy provided "Notice" with respect to its proposed generic copies of OxyContin® and the '799, '800, and '072 patents under 21 U.S.C. § 355(j)(2)(B).

25. Ranbaxy's submission of its ANDA was an act of infringement of the '799, '800, and '072 patents under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

26. Upon information and belief, Ranbaxy's proposed generic copies of OxyContin® are covered by one or more claims of the '799, '800, and '072 patents.

27. Upon information and belief, Ranbaxy's commercial manufacture, use, sale, and/or offer for sale of its proposed generic copies of OxyContin® would infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '799, '800, and '072 patents.

28. Upon information and belief, Ranbaxy has been aware of the existence of the '799, '800, and '072 patents, and has no reasonable basis for believing that its proposed generic copies of OxyContin® will not infringe the '799, '800, and '072 patents, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

29. The acts of infringement by Ranbaxy 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 Ranbaxy has infringed the '799, '800, and '072 patents, and that the commercial sale, offer for sale, use, and/or manufacture of its proposed generic copies of OxyContin® described in ANDA No. 202427 would infringe, induce infringement of, and/or contribute to the infringement of the '799, '800, and '072 patents;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 202427, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date not earlier than the dates of expiration of the '799, '800, and '072 patents plus any additional periods of exclusivity;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Ranbaxy, its officers, partners, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities and all other persons acting in concert, participation, or in privity with them, and their

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 '799, '800, and '072 patents;

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

E. Awarding Plaintiffs such other and further relief as this Court may deem just and proper.

Dated: October 7, 2011

ROPES & GRAY LLP

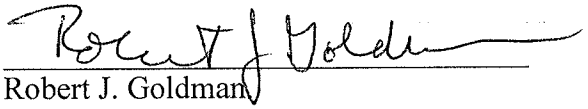

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EXHIBIT A

US007674799B2

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

(10) **Patent No.: US 7,674,799 B2**
(45) **Date of Patent: *Mar. 9, 2010**

(54) **OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE**

(75) Inventors: **Robert Chapman**, North Kingstown, RI (US); **Lonn S. Rider**, Foster, RI (US); **Qi Hong**, Sharon, MA (US); **Donald Kyle**, Newtown, PA (US); **Robert Kupper**, Coventry, RI (US)

(73) Assignee: **Purdue Pharma L.P.**, Stamford, CT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/653,531**

(22) Filed: **Jan. 16, 2007**

(65) **Prior Publication Data**

US 2007/0117831 A1 May 24, 2007

Related U.S. Application Data

(63) Continuation of application No. 11/391,897, filed on Mar. 29, 2006, which is a continuation of application No. 11/093,626, filed on Mar. 30, 2005, now Pat. No. 7,129,248.

(60) Provisional application No. 60/557,492, filed on Mar. 30, 2004, provisional application No. 60/601,534, filed on Aug. 13, 2004, provisional application No. 60/620,072, filed on Oct. 18, 2004, provisional application No. 60/648,625, filed on Jan. 31, 2005, provisional application No. 60/651,778, filed on Feb. 10, 2005.

(51) **Int. Cl.**
A61K 31/485 (2006.01)
C07D 489/08 (2006.01)

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

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

See application file for complete search history.

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Primary Examiner—Charanjit S Aulakh
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

In certain embodiments the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm of 14-hydroxycodeinone.

19 Claims, 5 Drawing Sheets

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Interference No. 105,553, Chapman Notice of Real Party-in-Interest, May 3, 2007.
Interference No. 105,553, Casner Identification of Related Proceedings, May 3, 2007.
Interference No. 105,553, Casner Identification of Real Party in Interest, May 3, 2007.
Interference No. 105,553, Casner Clean Claims, May 3, 2007.
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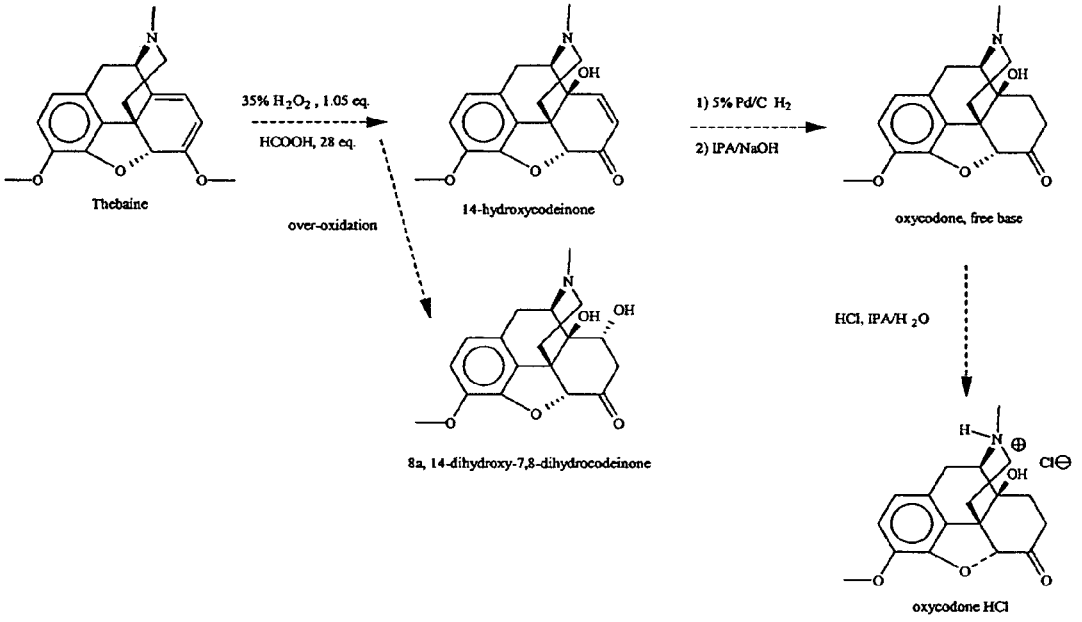
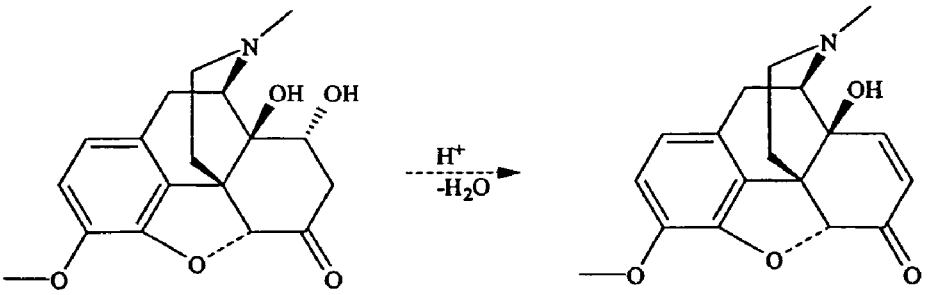
Interference No. 105,553, Exhibit 1042, Jan. 31, 2008.

FIGURE 1



Reaction scheme of the process used to produce oxycodone HCl from thebaine.

FIGURE 2



8a,14-dihydroxy-7,8-dihydrocodeinone

14-hydroxycodeinone

Dehydration of 8α, 14-dihydroxy-7,8-dihydrocodeinone

FIGURE 3

Typical HPLC Chromatogram of RTM Solution

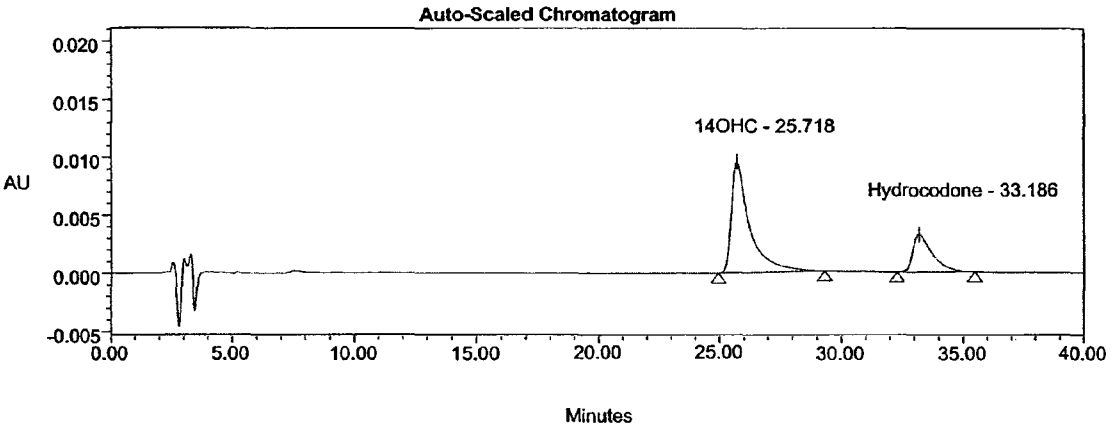


Figure 4

Typical HPLC Chromatogram of the Working 100 PPM 14OHC Standard Solution

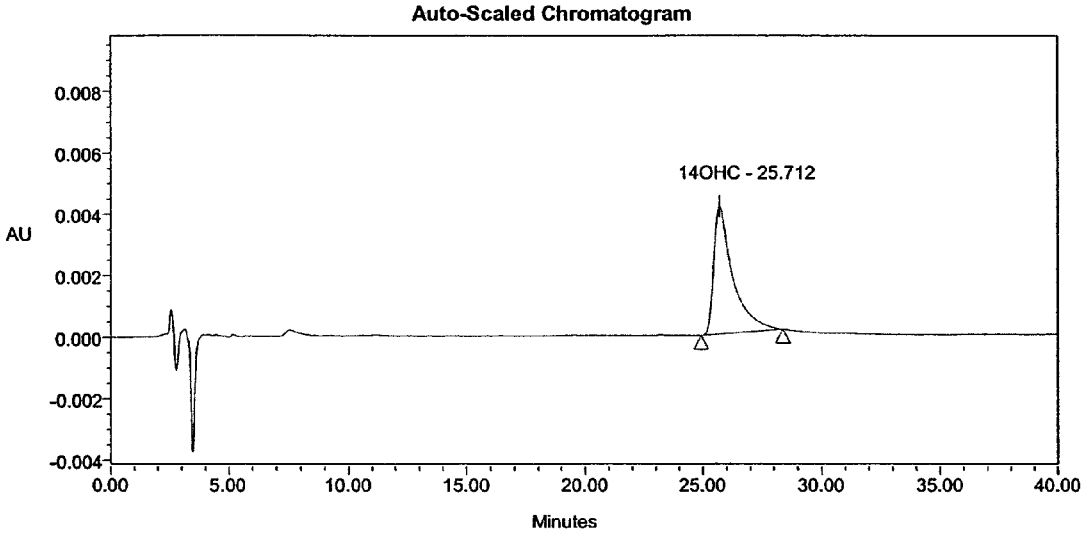
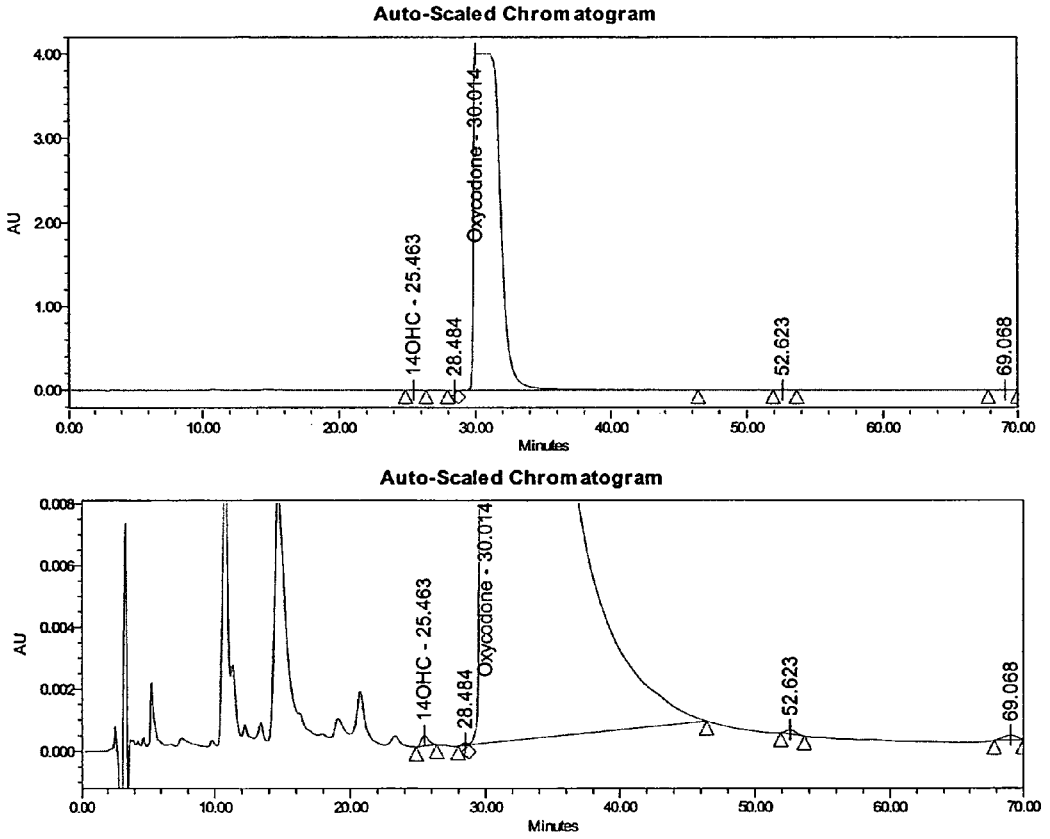


FIGURE 5

Typical HPLC Chromatogram of the Sample Solution containing Oxycodone API



OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE

This application is a continuation of U.S. patent application Ser. No. 11/391,897, filed Mar. 29, 2006. which is a continuation of U.S. patent application Ser. No. 11/093,626, filed Mar. 30, 2005, now U.S. Pat. No. 7,129,248, which claims priority to U.S. Provisional Application No. 60/651,778, filed Feb. 10, 2005, U.S. Provisional Application No. 60/648,625, filed Jan. 31, 2005, U.S. Provisional Application No. 60/620,072, filed Oct. 18, 2004, U.S. Provisional Application No. 60/601,534, filed Aug. 13, 2004, and U.S. Provisional Application No. 60/557,492, filed Mar. 30, 2004, all of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to a process for reducing the amount of 14-hydroxycodeinone in an oxycodone hydrochloride preparation.

BACKGROUND OF THE INVENTION

Oxycodone is a semi-synthetic opioid analgesic that exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, oxycodone may produce any of a variety of effects including analgesia.

Purdue Pharma L.P currently sells sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the trade name OxyContin®.

U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912; and 5,656,295 disclose sustained release oxycodone formulations.

Thebaine, a compound derived from opium, although having no medicinal use in itself, is useful as a starting material in synthetic schemes for the production of oxycodone. In other schemes, codeine can be utilized as the starting material for the production of oxycodone. 14-hydroxycodeinone is the immediate precursor to oxycodone in these schemes.

Methods of producing thebaine or 14-hydroxy substituted opium derivatives have been reported, e.g. in U.S. Pat. Nos. 3,894,026 and 4,045,440.

The oxidation of codeine to codeinone, an initial step in the synthesis of opium derivatives has been reported in EP 0889045, U.S. Pat. No. 6,008,355 and in the J. Am. Chem. Soc., 1051, 73, 4001 (Findlay).

The reaction of codeinone to 14-hydroxycodeinone has been reported in U.S. Pat. No. 6,008,355 and in Tetrahedron 55, 1999 (Coop and Rice).

The methylation of codeinone to thebaine has been reported in Heterocycles, 1988, 49, 43-7 (Rice) and EP0889045.

U.S. Pat. No. 6,177,567 describes the hydrogenation of 14-hydroxycodeinone to oxycodone by reduction with diphenylsilane and Pd(Ph3P)/ZnCl2 or with sodium hypophosphite in conjunction with a Pd/C catalyst in aqueous acetic acid.

Krabnig et al. in "Optimization of the Synthesis of Oxycodone and 5-Methyloxycodone" Arch. Pharm. (1996), 329 (6), (325-326) describes hydrogenating a solution of 14-hydroxycodeinone in glacial acetic acid with a Pd—C-catalyst at 30 psi at the described conditions.

During the oxidation of thebaine to give 14-hydroxycodeinone, several overoxidized products are formed including 8,14-dihydroxy-7,8-dihydrocodeinone. In the production of oxycodone free base from the 14-hydroxycodeinone, the 8,14-dihydroxy-7,8-dihydrocodeinone is carried though the process. During conversion of the oxycodone free base to oxycodone hydrochloride, the impurity undergoes acid-catalyzed dehydration and is converted into 14-hydroxycodeinone. Thus, 14-hydroxycodeinone is present in the final oxycodone hydrochloride composition. Oxycodone hydrochloride API (active pharmaceutical ingredient) is available from a variety of manufacturers such as Johnson Matthey and Mallinckrodt. Current commercially-available oxycodone hydrochloride API, and oxycodone hydrochloride prepared by known procedures, have a level of 14-hydroxycodeinone of greater than 100 ppm.

There is a continuing need in the art to provide an oxycodone hydrochloride composition that contains reduced amounts of 14-hydroxycodeinone as compared to compositions known in the art.

All references cited herein are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of certain embodiments of the present invention to provide a process for reducing the 14-hydroxycodeinone in an oxycodone hydrochloride composition to an amount of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is an object of certain embodiments of the present invention to provide a process for reacting an oxycodone base composition with hydrochloric acid under conditions to produce an oxycodone hydrochloride composition having an amount of 14-hydroxycodeinone of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is a further object of certain embodiments of the present invention to provide an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is a further object of certain embodiments of the present invention to provide a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm by reacting an oxycodone base composition with hydrochloric acid under conditions suitable to promote dehydration of 8,14-dihydroxy-7,8-dihydrocodeinone to 14-hydroxycodeinone during salt formation and under reducing conditions so as to convert thel4-hydroxycodeinone to oxycodone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising reacting an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of more than 100 ppm under conditions that reduce the amount of 14-hydroxycodeinone to a level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments, the invention is directed to an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising subjecting an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of greater than 100 ppm to hydrogenation to an extent that the amount of 14-hydroxycodeinone in the composition is reduced to an

amount of less than less 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments disclosed herein, the oxycodone composition having a 14-hydroxycodeinone level of less than 25 ppm can be subsequently hydrogenated to further decrease the amount of 14-hydroxycodeinone, e.g., from about 15 ppm to about 10 ppm or less.

In one embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of 100 ppm or higher, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm. In another embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of between 15 ppm and 25 ppm, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than about 10 ppm, or less than about 5 ppm. In another embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of between 10 ppm and 25 ppm, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than about 5 ppm.

In certain embodiments of the present invention, the process for preparing the oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprises hydrogenating the starting material under reflux. In certain embodiments, the process further comprises recovering the resultant oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising hydrogenating under reflux, a starting oxycodone hydrochloride composition having a 14-hydroxycodeinone level of greater than 100 ppm in a suitable solvent for a time sufficient to produce an oxycodone composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm; and recovering the oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm by crystallization and removal from the solvent (e.g., by filtration).

In certain embodiments, the oxycodone hydrochloride composition of the present invention has a lower limit of 0.25 ppm, 0.5 ppm, 1 ppm, 2 ppm or 5 ppm of 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising reacting in a suitable solvent an oxycodone base composition with hydrochloric acid in an amount greater than 1.0 molar equivalent as compared to the oxycodone base composition, the reacting step being performed under reducing conditions, to form an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising hydrogenating a 14-hydroxycodeinone composition to obtain an oxycodone free base composition; converting the oxycodone free base composition to oxycodone hydrochloride; and hydrogenating the oxycodone hydrochloride to obtain an oxycodone composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising hydrogenating a 14-hydroxycodeinone composition to obtain an oxycodone free base composition; converting the oxycodone free base composition to oxycodone hydrochloride; isolating the oxycodone hydrochloride; and hydrogenating the oxycodone hydrochloride to obtain an oxycodone composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising oxidizing a thebaine composition to form 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition; hydrogenating the 14-hydroxycodeinone composition to form an oxycodone base composition; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing 14-hydroxycodeinone comprising oxidizing a thebaine composition to form 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition;

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising reacting an oxycodone base composition with an acid having a higher pH than hydrochloric acid to form a corresponding acid addition salt of oxycodone, and converting the acid addition salt of oxycodone to oxycodone hydrochloride.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising contacting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone with a substance that preferentially removes the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising subjecting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone to chromatographic separation to preferentially removes the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising reacting in a suitable solvent an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone, with boronated polystyrene resin; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising reacting in a suitable solvent an oxycodone base

composition with boronated polystyrene resin; and converting the oxycodone base composition to an oxycodone hydrochloride composition.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising combining hydrochloric acid and an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone in a solvent to form a solution; and spray drying the solution to generate oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising combining hydrochloric acid and an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone in a solvent to form a solution; and lyophilizing the solution to generate oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising combining hydrochloric acid and an oxycodone base composition in a solvent to form a solution; and spray drying the solution to generate oxycodone hydrochloride.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising combining hydrochloric acid and an oxycodone base composition in a solvent to form a solution; and lyophilizing the solution to generate oxycodone hydrochloride. The term "bulk" means an amount of material of at least 1 kg. In certain embodiments, the amount can be from about 10 kg to about 1000 kg or from about 10 kg to about 500 kg. In certain embodiments, the amount is in an amount of from about 20 kg to about 100 kg; about 20 kg or about 50 kg. Bulk oxycodone hydrochloride composition can be packaged, e.g., in a pharmaceutically acceptable package such as corrugated box containers (made of, e.g., plastic and/or paper); in drums (made of, e.g., a metal or metal composite material); or in bags of woven fabric generally referred to as flexible intermediate bulk containers (FIBCs). Each of these approaches use various configurations of liners, typically made of polyethylene or polypropylene, that fit within the corrugated box, drum, or within the FIBC for preventing contamination of the product being shipped. Preferably, these packaging approaches use containers configured to be supported by and carried on pallets.

The term "ppm" as used herein means "parts per million". As used to refer to 14-hydroxycodeinone, "ppm" means parts per million of 14-hydroxycodeinone in a particular sample.

The term 8,14-dihydroxy-7,8-dihydrocodeinone includes either 8α,14-dihydroxy-7,8-dihydrocodeinone; or 8β,14-dihydroxy-7,8-dihydrocodeinone or can include a mixture of both compounds.

The oxycodone hydrochloride preparation can be, e.g., an oxycodone active pharmaceutical ingredient (API), such as oxycodone hydrochloride U.S.P., uncombined or combined with one or more other ingredients. For example, the oxycodone preparation can be a final pharmaceutical dosage form, or an intermediate preparation for a final dosage form, that can be tested for the presence of 14-hydroxycodeinone and/or codeinone, e.g., for quality assurance purposes. Preferably, the oxycodone hydrochloride preparation is oxycodone hydrochloride API and contains at least 95% oxycodone hydrochloride, at least 98% oxycodone hydrochloride, at least 99% oxycodone hydrochloride, or at least 99.9% oxycodone hydrochloride.

The method of detecting the presence of 14-hydroxycodeinone in an oxycodone preparation can be performed in accordance with commonly assigned U.S. Provisional Application Ser. No. 60/557,502, entitled "Methods For Detecting 14-Hydroxycodeinone" filed Mar. 29, 2004 and in accordance with U.S. Provisional Application entitled "Methods For Detecting 14-Hydroxycodeinone" filed Jan. 31, 2005.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic of a reaction of thebaine to oxycodone hydrochloride, including the oxidation of thebaine to 14-hydroxycodeinone and the 8,14-dihydroxy-7,8-dihydrocodeinone impurity.

FIG. **2** is a schematic of the dehydration of 8,14-dihydroxy-7,8-dihydrocodeinone to 14-hydroxycodeinone.

FIG. **3** depicts a separation of the system suitability testing solution of Example 4.

FIG. **4** depicts a HPLC chromatogram for the Working 100 PPM 14OHC Standard Solution of Example 4.

FIG. **5** depicts typical HPLC chromatogram for the Oxycodone API Sample Solution of Example 4.

DETAILED DESCRIPTION

In certain embodiments, the invention is directed to a process for reducing the amount of 14-hydroxycodeinone in an oxycodone hydrochloride composition (e.g., oxycodone hydrochloride API), and to the resultant oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm recovered from that process. In certain embodiments, the present invention is directed to a process for reducing the amount of 14-hydroxycodeinone in an oxycodone hydrochloride composition comprising reacting the oxycodone hydrochloride composition with a catalytically effective amount of a transition metal compound and a gas comprising hydrogen, at a temperature and for a period of time sufficient to reduce the content of 14-hydroxycodeinone to a level wherein the resultant oxycodone hydrochloride composition comprises 14-hydroxycodeinone in an amount less than 25 ppm, less than about 15 ppm; less than about 10 ppm, or less than about 5 ppm.

The process of the present invention also may result in the reduction of other alpha, beta, unsaturated ketones in oxycodone compositions, in addition to 14-hydroxycodeinone such as, e.g., codeinone.

In accordance with certain embodiments of the present invention, an oxycodone hydrochloride composition (e.g., oxycodone hydrochloride API), and a solvent, are fed into a reaction apparatus. The composition is then hydrogenated under adequate conditions for a sufficient period; the catalyst is removed from the solvent; and the oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm is isolated and removed, e.g., by crystallization and filtration.

Hydrogenation of the 14-hydroxycodeinone in the processes of the present invention can be accomplished by using, e.g., pressurized-catalytic hydrogenation or catalytic transfer hydrogenation in an appropriate acid, e.g., acetic acid. A particular hydrogenation reaction employs hydrogen gas or $NaHPO_2$ along with a palladium-carbon catalyst. In certain embodiments, a hydrogen donor for use in the hydrogenation of the 14-hydroxycodeinone can be selected from hydrogen, primary and secondary alcohols, primary and secondary

amines, carboxylic acids and their esters and amine salts, readily dehydrogenatable hydrocarbons (e.g., lower alkyl-substituted aromatic hydrocarbons such as ethylbenzene, diethylbenzene, isopropylbenzene, diisopropylbenzene, o-ethyltoluene, m-ethyltoluene, p-ethyltoluene, o-isopropyltoluene, m-isopropyltoluene, p-isopropyltoluene, ethylnaphthalene, propylnapththalene, isopropylnaphthalene, and diethylnaphthalene; paraffins such as ethane, propane, n-butane, isobutane, n-pentane, isopentane, n-hexane, n-heptane, n-octane, n-nonane, n-decane, and branched chain isomers thereof; cycloparaffins such as cyclobutane, cyclopentane, cyclohexane, methylcyclopentane, methylcyclohexane, and ethylcyclopentane; olefins such as ethylene, propylene, 1-butene, 2-butene, 1-pentene, 2-pentene, 1-hexene, 2-hexene, 3-hexene, and branched chain derivatives thereof), clean reducing agents (e.g., polymer-supported organotin hydrides, and any suitable combination thereof. In certain embodiments, the hydrogenation can be performed as disclosed in U.S. Provisional Application No. 60/477,968, filed Jun. 12, 2003, entitled "Hydrogenation of Opioids Without Hydrogen Gas Feed."

In certain embodiments, the hydrogenation is carried out at a pressure from about 5 PSIG to about 200 PSIG, or from about 40 PSIG to about 60 PSIG. In certain embodiments, the hydrogenation is carried out at a temperature of from about 20° C. to about 100° C., or from about 40° C. to about 85° C.

In certain embodiments, the hydrogenation is carried out at a pH of less than 5, less than 3, or less than 1, e.g., about 0.5.

In certain embodiments of the present invention, the 14-hydroxycodeinone is converted to oxycodone by hydrogenation utilizing diphenylsilane and $Pd(Ph_3P)/ZnCl_2$ and sodium hypophosphite in conjunction with a Pd/C catalyst in aqueous organic acid; or Pd/C catalytic transfer hydrogenation.

The total reaction time of the hydrogenation reaction is for a duration sufficient to reduce the content of the 14-hydroxycodeinone to a level that is less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm. The actual reaction time can vary depending upon the temperature and efficiency of the hydrogenation system. Depending on the hydrogenation conditions (e.g., temperature and pressure), the total reaction time to achieve the desired reduction in 14-hydroxycodeinone can be, e.g., from about 10 minutes to about 36 hours. The hydrogenation of the 14-hydroxycodeinone can be carried out in the presence of a noble metal catalyst. In certain embodiments, suitable catalysts can be selected from Raney cobalt, Raney nickel, palladium on carbon, platinum on carbon, palladium on alumina, platinum oxide, ruthenium on alumina, rhodium on alumina, or rhodium on carbon, among others. One particular catalyst for this reduction is 5% palladium on carbon. The quantity of palladium on carbon catalyst can be from about 0.05% w/w to about 50% w/w, or from about 0.5% w/w to about 5%, in relation to the treated composition.

The reaction may be carried out in a solvent such as water; an alcohol (such as, e.g., isopropanol, methanol or ethanol); tetrahydrofuran; an aromatic hydrocarbon (such as benzene); an ether (such as dioxane); an ester of a lower alkanoic acid (such as methyl acetate or ethyl acetate); an amide (such as, e.g., dimethylformamide, diethylformamide, dimethylacetomide, or other N-alkyl substituted lower fatty acid amides); N-methylpyrrolidone; formylmorpholine; β-methoxypropionitrile; a carboxylic acid (such as formic, acetic, propionic acid or other lower alkanoic acid) or an appropriate mixture of any two or more of the aforementioned solvents. One particular co-solvent combination is isopropanol/water.

In certain embodiments, the solvent is typically mixed with the 14-hydroxycodeinone-containing composition (e.g., an oxycodone composition) prior to hydrogenation.

In certain embodiments, the invention is directed to the conversion of an oxycodone free base composition (with an 8,14-dihydroxy-7,8-dihydrocodeinone component) to oxycodone hydrochloride. During salt formation reactions known in the art, the 8,14-dihydroxy-7,8-dihydrocodeinone component is converted to 14-hydroxycodeinone by acid-catalyzed dehydration. Thus, 14-hydroxycodeinone is increased in the final product. By virtue of the present invention, this can be reduced by overloading the amount of hydrochloric acid in the salt formation to promote the reaction of 8,14-dihydroxy-7,8-dihydrocodeinone to 14-hydroxycodeinone and providing reducing conditions sufficient for the 14-hydroxycodeinone to be readily converted to oxycodone. In such an embodiment, the amount of hydrochloric acid is an amount of greater than 1 molar equivalent as compared to the oxycodone free base. In certain embodiments, the molar equivalent amount of hydrochloric acid can be greater than about 1.2 molar equivalents or greater than about 1.4 molar equivalents. In certain embodiments, the amount of hydrochloric acid can be about 1.5 molar equivalents. The reducing conditions sufficient to drive the 14-hydroxycodeinone to oxycodone can be provided, e.g., by a catalyst with a hydrogen donor.

Further, during salt formation, the rate of dehydration of 8,14-dihydroxy-7,8-dihydrocodeinone to 14-hydroxycodeinone is reduced as the pH of the solution increases. Therefore, in certain embodiments, the pH of the solution can be adjusted to a pH of from about 1.5 to about 2.5, preferably to about 1.8, (e.g., from a pH of less than 1) with a suitable basic agent, e.g., sodium hydroxide. This further minimizes the formation of 14-hydroxycodeinone from 8,14-dihydroxy-7,8-dihydrocodeinone during crystallization. Preferably, the pH adjustment is performed after the hydrogenation step and prior to removal of catalyst and isolation of the oxycodone having a 14-hydroxycodeinone level of less than 25 ppm.

In certain embodiments it may be necessary to perform the process of the present invention, or one or more relevant steps in the process of the present invention, more than once in order to reduce the amount of 14-hydroxycodeinone to a desired level, e.g., less than about 10 ppm, or less than about 5 ppm.

In certain embodiments of the present invention, oxycodone hydrochloride compositions can be prepared by certain alternative processes. Such alternative processes preferably result in an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm. One such alternative process is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising oxidizing a thebaine composition to form 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition; hydrogenating the 14-hydroxycodeinone composition to form an oxycodone base composition; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

Another alternative process is directed to a process for preparing 14-hydroxycodeinone comprising oxidizing a thebaine composition to form a 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition com-

prising reacting an oxycodone base composition with an acid having a higher pH than hydrochloric acid to form a corresponding acid addition salt of oxycodone, and converting the acid addition salt of oxycodone to oxycodone hydrochloride. In such an embodiment, the acid may be selected from the group consisting of tartaric acid, oxalic acid, fumaric acid, phosphoric acid, sulfuric acid and mixtures thereof.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising contacting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone with a substance that preferentially removes the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone. In preferred embodiments the contacting substance can be a gel. In further embodiments, the contacting can comprise passing a solution comprising the oxycodone base composition through the substance or can comprise forming a slurry with the oxycodone base composition and the gel.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising subjecting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone to chromatographic separation to preferentially remove the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone. In preferred embodiments, the chromatographic separation is a simulated moving bed.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising contacting an oxycodone hydrochloride composition having an amount of 14-hydroxycodeinone with a substance that preferentially removes the 14-hydroxycodeinone as compared to the oxycodone hydrochloride; and recovering an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone. In preferred embodiments the contacting substance can be a gel. In further embodiments, the contacting can comprise passing a solution comprising the oxycodone hydrochloride composition through the substance or can comprise forming a slurry with the oxycodone hydrochloride composition and the gel.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising subjecting an oxycodone hydrochloride composition having an amount of 14-hydroxycodeinone to chromatographic separation to preferentially remove the 14-hydroxycodeinone as compared to the oxycodone hydrochloride; and recovering an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone. In preferred embodiments, the chromatographic separation is a simulated moving bed.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising reacting in a suitable solvent an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone, with boronated polystyrene resin; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone. Preferably the reacting is performed at a temperature below about 20 degrees C.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition comprising reacting in a suitable solvent an oxycodone base composition with boronated polystyrene resin; and converting the oxycodone base composition to an oxycodone hydrochloride composition. Preferably the reacting is performed at a temperature below about 20 degrees C.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising combining hydrochloric acid and an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone in a solvent to form a solution; and spray drying the solution to generate oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising combining hydrochloric acid and an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone in a solvent to form a solution; and lyophilizing the solution to generate oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition comprising combining hydrochloric acid and an oxycodone base composition in a solvent to form a solution; and spray drying the solution to generate oxycodone hydrochloride.

Another alternative process is directed to a process for preparing an oxycodone hydrochloride composition comprising combining hydrochloric acid and an oxycodone base composition in a solvent to form a solution; and lyophilizing the solution to generate oxycodone hydrochloride.

Further Embodiments

The oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubri-

cating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, suppositories, solutions, suspensions, etc.

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

When the dosage form is oral, the dosage form of the present invention contains from about 10 mg to about 320 mg of oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm. Particularly preferred dosages for twice daily dosing are about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 80 mg, about 100 mg, or about 160 mg. Particularly preferred dosages for once daily dosing are about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 160 mg, or about 320 mg. The oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release of the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm. Such formulations can be prepared in accordance with U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912; and 5,656,295.

The oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material which is incorporated into a matrix along with the oxycodone or salt thereof.

The sustained release dosage form may optionally comprise particles containing oxycodone having a 14-hydroxycodeinone level of less than 25 ppm. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

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

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

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

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

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

Plasticized hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

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

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

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

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

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

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

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,8989; 4,063,064; and 4,088,864.

Matrix Formulations

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

For example, a matrix in addition to the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm may include:

Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols.

Of these polymers, acrylic polymers, especially Eudragit® RSPO—the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

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

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

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

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 2530° to about 200° C., preferably from about 45° C. to about 90° C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and camauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 25° to about 100° C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, camauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxycodone hydrochloride release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodi-

ments 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 opioidoxycodone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

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

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

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

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

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

Matrix—Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm; (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 hydroxalkyl cellulose granules with water.

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

Melt Extrusion Matrix

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

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

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

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

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

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm, and an optional binder; heating the homogenous mixture; extruding

the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

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

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

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

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

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

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

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

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

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

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

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

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include those described in U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712.

Alkylcellose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or

alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

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

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

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

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

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

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

Plasticizers

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

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

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

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be

formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. Nos. 4,200,098 and 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n.H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm thereof from the osmotic dosage form.

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

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

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

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

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm.

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

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr·atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across

the semipermeable wall. Other polymers useful in the present invention are known in the art in U.S. Pat. Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

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

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

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm equivalent to 10 to 40 mg oxycodone hydrochloride, 25 to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm. Preparation of sustained release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

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

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

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

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

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

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

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

Additional Embodiments

The oxycodone hydrochloride having a 14-hydroxycodeinone level of less than 25 ppm may be used as a substitute for the oxycodone hydrochloride in any existing commercial product such as, e.g., Tylox®, Roxilox®, Roxicet®, Percocet®, Oxycet®, Percodan®, Roxycodone®, OxyContin® and OxyIR®. Such formulations are listed in the PDR 58th Edition (2004) and the FDA Orange Book.

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

Example 1

In Example 1, 37.7 g of oxycodone HCl (35.4 g dry basis, ca. 500 ppm 14-hydroxycodeinone) was placed in a 500 mL Parr reaction bottle and combined with 0.55 g 5% Pd/C catalyst, 50% water wet (Johnson Matthey type 87L), and 182.2 g of 61.9% isopropanol/water (w/w). The mixture was placed under an inert atmosphere and heated with shaking to 45-50° C. Upon dissolution of all starting material, the pressure in the bottle was vented to the atmosphere and hydrogen pressure was applied (45 PSIG) for 4 hours. At the end of the hydrogenation, the hydrogen was vented off and the solution was allowed to cool to room temperature.

The next day, the mixture was heated to 75° C. to dissolve the crystallized solids and then suction filtered over a 0.2 μm PTFE membrane into a 1 L jacketed cylindrical flask

(equipped with a condenser, a nitrogen atmosphere, a mechanical stirrer, a type K thermocouple, and a programmable refrigerated recirculator). The Parr bottle was rinsed with deionized water (11.7 g), which was added to the 1 L flask through the filter. Isopropanol (334.7 g) was added to the flask and the mixture was re-heated with stirring to 75° C. and held to dissolve any crystallized solids. The solution was cooled with stirring to 0-10° C. over 8 hours (linear ramp) and held at 0-10° C. for 20 hours. The crystallized solid was then collected by suction filtration and washed with 107 g of cold 95:5 isopropanol/water (w/w).

To remove isopropanol from product, the solvent-wet material was transferred to a drying dish and placed in a vacuum desiccator with an open container of deionized water. The solid was held in this manner, under vacuum, overnight. The material was then dried under vacuum at 60° C.

Analysis of the dried material using the low 14-hydroxycodeinone method of Example 4 below gave a result of 6 ppm of 14-hydroxycodeinone.

Analysis of the dried material using the method of Example 6 below gave a result of <5 ppm of codeinone and 8 ppm of 14-hydroxycodeinone.

Example 2

In Example 2, 35.0 g of oxycodone HCl (33.3 g dry basis, ca. 4000 ppm 14-hydroxycodeinone) was placed in a 500 mL Parr reaction bottle and combined with 0.49 g 5% Pd/C catalyst, 50% water wet (Johnson Matthey type 87L), and 159.9 g of 62.3% isopropanol/water. The mixture was placed under an inert atmosphere and then heated with shaking to 45-50° C. Upon dissolution of the starting material, the pressure in the bottle was vented to the atmosphere and hydrogen pressure was applied (45 PSIG). After 5.25 hours of shaking, the hydrogen was vented off, and the solution was allowed to cool to room temperature. The mixture was re-heated the next day and hydrogenation was continued for 4.75 hours.

The mixture was heated to 75° C. and then suction filtered over a 0.2 μm PTFE membrane into a 1 L jacketed cylindrical flask (equipped with a distillation head, a nitrogen atmosphere, a mechanical stirrer, a type K thermocouple, and a programmable refrigerated recirculator). The Parr bottle was rinsed with deionized water (11.7 g), which was added to the 1 L flask through the filter.

Isopropanol (295.6 g) was added to the flask and the mixture was heated to boiling (ca. 81° C.). To remove water and increase the yield, isopropanol/water azeotrope was distilled from the flask until 305.7 g had been collected. Fresh isopropanol (305.6 g) was added and the distillation head was removed and replaced with a condenser.

The mixture was cooled with stirring from boiling to 0-10° C. over 8 hours (linear ramp) and held at 0-10° C. for 20 hours. The crystallized solid was then collected by suction filtration and washed with 107 g of cold 95:5 isopropanol/water. The material was dried as described in Example 1.

Analysis of the dried material using the low 14-hydroxycodeinone method of Example 4 below gave a result of <5 ppm of 14-hydroxycodeinone.

Analysis of the dried material using the method of Example 6 below gave a result of <5 ppm of codeinone and <5 ppm of 14-hydroxycodeinone.

Example 3

In Example 3, 27.83 g of oxycodone free-base, water wet (24.57 g dry basis, 0.0779 mol, ca. 3000 ppm 14-hydroxycodeinone), 39.8 g of deionized water, 81.9 g of isopropanol, 0.49 g 5% Pd/C catalyst, 50% water wet (Johnson Matthey type 87L), and conc. HCl (11.3 g, 0.117 mol, 1.50 equivalents based on 37.7% HCl assay) were combined in a 500 ml Parr shaker bottle.

The mixture was placed under an inert atmosphere and heated to 75° C. with shaking. The pressure in the bottle was relieved, and the system was pressurized with hydrogen (45 PSIG). The solution was held under these conditions for 21.7 hours. Analysis by HPLC showed that the ratio of the area of the 8,14-dihydroxy-7,8-dihydrocodeinone peak to that of oxycodone was reduced from 0.29% to 0.04% during this time.

The hydrogen pressure was vented and the system was placed under an inert atmosphere. In order to prevent further dehydration of any residual 8,14-dihydroxy-7,8-dihydrocodeinone, the pH of the solution was adjusted from 0.5 to 1.8 with 20.7 g NaOH saturated isopropanol (some solid sodium hydroxide was also present).

The solution was re-heated to 75° C. and then pressure filtered through a 0.2 μm PTFE membrane filter housed in heat-traced 47 mm SS filter holder into a 500 ml jacketed cylindrical reactor (condenser, N_2, mechanical stirrer, programmable refrigerated recirculator). The Parr bottle was rinsed with 8.6 g of deionized water, which was added to the flask through the filter.

Isopropanol (222.5 g) was added to the solution in the flask and the resulting slurry was heated to approximately 75° C. to re-dissolve the solids. After reaching the desired temperature, the solution was held for two hours (to simulate typical processing times). No 14-hydroxycodeinone was detected in a sample of the crystallization mixture after this hold.

The circulator was set to cool from 80° C. to 0° C. over 8 hours. Approximately 24 hours after starting the cooling program, the solids were collected by suction filtration and washed three times with 95:5 isopropanol/water (232.8 g total). The material was dried as described in Example 1.

Analysis of the dried material using the low 14-hydroxycodeinone method of Example 4 below gave a result of 5 ppm of 14-hydroxycodeinone.

Analysis of the dried material using the method of Example 6 below gave a result of <5 ppm of codeinone and 10 ppm of 14-hydroxycodeinone.

Example 4

Analysis of sample to determine 14-hydroxycodeinone level.

The products of Examples. 1-3 were analyzed to determine the level of 14-hydroxycodeinone under 100 parts per million (PPM) level by a HPLC method using a Waters Atlantis 5 μm dC18, 3×250 mm column maintained at 50° C. and isocratic elution using pH 9.35, 17 mM ammonium carbonate buffer and methanol (60:40). Quantitation was achieved by measuring the peak area response with UV detection at 220 nm using external standard. This method utilized mobile phase with volatile components that are compatible with LC/MS analysis.

The reagents used were as follows:

1. Ammonium carbonate, analytical reagent grade (Aldrich);
2. Water, HPLC grade;
3. Methanol, HPLC grade;
4. Acetic acid, reagent grade (J. T Baker Glacial Acetic Acid);
5. Ammonium hydroxide, reagent grade;
6. Phosphoric acid, about 85%, A.C.S. reagent;

7. 14-Hydroxycodeinone reference material from Albany Molecular Research, Inc.

The equipment used was as follows:

A. HPLC System

1. HPLC system capable of delivering 0.4 mL/minute of mobile phase (Waters Alliance);

2. UV/Visible detector set to monitor the eluant at 220 nm (Waters 2487 UV/Vis);

3. Autosampler capable of injecting 6 μL;

4. Integrator or suitable data recording system (Waters Millennium 32 chromatograph system.);

5. Waters, Atlantis dC18 column, 3×250 mm, 5 μm;

6. Column heater capable of maintaining a constant temperature of 50° C.;

7. On-line vacuum degasser.

B. Equipment for Mobile Phase Preparation

1. pH meter, preferably with automatic temperature compensation (ATC);

2. Ultrasonic bath, Model 5200, Branson;

3. 0.45-μm membrane filters for aqueous solvent, Whatman or Millipore, Cellulose acetate or Nylon.

Solutions

17 mM Ammonium Carbonate, pH 9.35

1.6±0.1 g of ammonium carbonate was weighed and placed into a 1-L beaker. 1000 mL of water was added to the beaker and stirred with a magnetic stirrer until the ammonium carbonate was dissolved. The pH was adjusted to 9.35-9.40 with ammonium hydroxide.

B. Mobile Phase

400 mL of HPLC-grade methanol was mixed with 600 mL of 17 mM ammonium carbonate, pH 9.35-9.40 prepared above. The mixture was filtered through solvent membrane filters and then degassed using an on-line vacuum degasser in the HPLC system.

C. 0.85% Phosphoric Acid Solution

10.0 mL of 85% H_3PO_4 was pipetted into a 1 liter volumetric flask and diluted to volume with water and mixed thoroughly.

D. 14-Hydroxycodeinone Working Reference Standard Solutions

A stock 14-hydroxycodeinone standard solution was prepared by weighing 25±2 mg of 14-hydroxycodeinone reference material and transferring it into a 250-mL volumetric flask. Approximately 100 mL of 0.85% H_3PO_4 solution was added to the flask and sonicated for approximately 2 minutes or until dissolved. The solution was diluted to volume with 0.85% H_3PO_4 solution and mixed thoroughly. This was the stock 14-hydroxycodeinone standard solution.

A working solution of 100 ppm 14-hydroxycodeinone standard solution for system suitability was prepared by pipetting 5.0 mL of the stock 14-hydroxycodeinone standard solution into a 100-mL volumetric flask, diluting the solution to volume with water and mixing thoroughly.

A working solution of 10 ppm 14-hydroxycodeinone standard solution for sensitivity was prepared by pipetting 5.0 mL of working 100 ppm 14-hydroxycodeinone standard solution into a 50-mL volumetric flask, diluting the solution to volume with water and mixing thoroughly.

A stock hydrocodone standard solution was prepared by weighing 25±2 mg of hydrocodone reference material and transferring contents into a 250-mL volumetric flask. Approximately 100 mL of 0.85% H_3PO_4 solution was added to the flask and sonicated for approximately 2 minutes or until dissolved. The solution was diluted to volume with 0.85% H_3PO_4 solution and mixed thoroughly.

E. Hydrocodone Working Reference Standard Solution

Stock Hydrocodone Standard Solution was prepared by weighing 25±2 mg of Hydrocodone reference material and transferring contents into a 250-mL volumetric flask. Approximately 100 mL of 0.85% H3PO4 solution was added to the flask and sonicated for approximately 2 minute or until dissolved. The solution was diluted to volume with 0.85% H3PO4 Solution and mixed thoroughly.

F. Sample Solutions

A sample solution was prepared by weighing about 250 mg oxycodone API sample into a scintillation vial. 5.0 mL of water was pipetted into the vial to dissolve the sample. The vial was tightly capped and sonicated for approximately 5 minutes or until the sample was dissolved. The contents were then shaken and mixed thoroughly.

G. Resolution Test Mixture (RTM) Solution

A solution containing two components, 14-hydroxycodeinone and hydrocodone, was prepared from the respective stock standard solutions.

The Resolution Test Mixture (RTM) was prepared by pipetting separately 10.0 mL of each stock standard solution of hydrocodone above and 14-hydroxycodeinone above into the same 100 mL volumetric flask and diluted to volume with a sufficient amount of water and mixed thoroughly.

H. HPLC Conditions

The HPLC conditions were as follows:

Column: Waters, Atlantis dC18, 3×250 mm, 5 μm.

Column temperature: 50° C.

Detector wavelength: 220 nm

Injection volume: 6 μl

Quantitation: Peak area of 14-hydroxycodeinone

Mobile Phase: (60:40) 17 mM ammonium carbonate, pH 9.35-9.40: Methanol

Flow rate: 0.4 mL/minute

Run time: 70 minutes for the samples and 40 minutes for the standard and RTM solutions

I. Resolution Test Mixture (RTM) Test

Before performing the system suitability test, a new column was equilibrated over night (at least 12 hours) by pumping mobile phase through it at 0.4 mL/min. After the new column was equilibrated, 6 μL of RTM solution was injected into the equilibrated system to ensure that the two eluted component peaks did not interfere with one another. A typical separation of the system suitability testing solution is shown in FIG. **3**.

J. System Suitability Test

A system suitability test was performed by injecting the Working 100 ppm 14-hydroxycodeinone standard solution into the system and by performing the system suitability test as described in the USP <621> by making six different runs of 6 μL injections. The system suitability test results met the following criteria listed in Table 1 below.

TABLE 1

Test No.	System Suitability Test	Specification
1	RSD of peak areas for 14-hydroxycodeinone (1)	RSD ≦3.0%
2	RSD of retention time for 14-hydroxycodeinone (1)	RSD ≦2.0%
3	Column Efficiency (Theoretical Plates of 14-hydroxycodeinone) (1)	N ≧ 2000

TABLE 1-continued

Test No.	System Suitability Test	Specification
4	Resolution between 14-hydroxycodeinone and Hydrocodone (2)	R ≧ 1.5
5	Signal to noise ratio (3)	S/N ≧10

Note:
(1) the working 100 ppm 14-hydroxycodeinone standard solution for Test Nos. 1 to 3 was used.
(2) the RTM for Test No. 4 was used.
(3) the working 10 ppm 14-hydroxycodeinone standard solution for Test No. 5 was used.

Before starting the experiment, 6 μL of water was injected to ensure that there were no interfering peaks co-eluting with the peak for 14-hydroxycodeinone. The following procedure was then conducted.

The working 100 ppm 14-hydroxycodeinone standard solution was injected six times in different runs, and the system was checked to verify that it met the system suitability test specifications as listed for Test Nos. 1, 2 and 3 in Table 1 above.

The RTM solution was injected and run once in the HPLC system to confirm that the system met the system suitability test specification as listed for Test No. 4 in Table 1 above.

The working 10 ppm 14-hydroxycodeinone standard solution was injected and run once in the HPLC system to confirm that the system had signal-to-noise ratio S/N greater than or equal to 10, as listed in the specification for Test No. 5 in Table 1 above.

After the system passed all of the above tests, the following HPLC procedure was performed.

The working 100 ppm 14-hydroxycodeinone standard solution and the working 10 ppm 14-hydroxycodeinone standard solution were each injected separately. Both working standard solutions were used to quantitate the samples. The setting and integration parameters are listed in Table 2 below.

TABLE 2

Integration Setting	Parameters
Minimum area	0
Minimum height	0
Threshold	2
Peak width	90.00
Inhibit integration: 0.01 to 20 minutes	Eliminates solvent front

Typical HPLC chromatograms for the working 100 ppm 14-hydroxycodeinone standard solution and the oxycodone API sample solution are shown in FIG. **4** and FIG. **5** respectively. Retention times of the 14-hydroxycodeinone and other related substances are presented in Table 3 below.

TABLE 3

Peak ID	Relative Retention Time vs. Oxycodone (RRT)
Oxycodone-N-Oxide (ONO)	0.16
Noroxycodone	0.31
Oxymorphone	0.45
7,8-Dihydro-8,14-Dihydroxycodeinone (DDC)	0.58
14-Hydroxycodeine	0.73
14-Hydroxycodeinone	0.79
6-α-Oxycodol	0.96
Hydrocodone	0.95
Oxycodone	1.0
Thebaine	1.89

The following calculations were performed using the results obtained above. Using Millennium®, software, the parameters were entered as follows:

In the sample set, the standard concentrations for both working standards (10 and 100 ppm) were calculated as follows:

$$100\ PPM\ \text{std.conc.} = \frac{W_{std}\ \text{corrected for purity}}{250} \times 0.05$$

$$10\ PPM\ \text{std.conc.} = \frac{W_{std}\ \text{corrected for purity}}{250} \times 0.005$$

where W_{std} is the weight of standard.

The following were also entered:

Sample weight=weight of sample in mg

Dilution=5 ml (sample dilution)

Label claim=0.0001 (to convert the results in PPM.

The amount of 14-hydroxycodeinone (abbreviated as OHC) in oxycodone sample in ppm can be determined automatically from a linear calibration curve using the two standards (100 PPM and 10 PPM) and the equation used in the calculation below.

$$PPM\ \text{of}\ 14\,OHC = \frac{A_{sam} - Y_{intercept}}{\text{Slope}}\ X\ \frac{D}{W_{sam}} \times 1000000$$

where:

A_{sam}=peak area of 14OHC

$Y_{intercept}$=Y intercept from a linear regression line using the two standards

Slope=slope from a linear regression line using the two standards

D=5.0 (sample dilution factor)

W_{sam}=sample weight in mg

1000000=Convention factor to convert the result to PPM

Example 5

3.0 g of oxycodone hydrochloric salt containing 154 ppm 14-hydroxycodeinone was dissolved in 20 mL water to afford a clear solution in a 250 mL Parr reaction bottle. To the solution, 0.05 g 5% Pd/C catalyst, 50% water wet (Johnson Matthey type 87L) and 1 mL formic acid 88% were added. The mixture was placed under inert atmosphere without hydrogen feed and then heated to 45° C.-50° C. After 2 hours of shaking, a sample was taken to check the disappearance of 14-hydroxycodeinone. The sample showed no 14-hydroxycodeinone by the HPLC method described in Example 4 above.

The solution was then suction filtered over a 0.2 micron PTFE membrane to remove the catalyst. An aliquot of 2 mL was taken out of about 18 mL filtrate solution. To this solution, 2.0 mL isopropyl alcohol was added to obtain a clear solution, followed by 4.0 mL of ethyl acetate. The solution was stirred, cooled and kept at 0-5° C. for 20 hours to afford oxycodone hydrochloride crystals. The crystalline solid was isolated by suction filtration. The wet solid was dried in an oven at 50° C. and 10 mmHg pressure. The dried solid weighed 0.12 g.

Analysis using the HPLC method in Example 4 above indicated that about 11 ppm 14-hydroxycodeinone were present in the oxycodone hydrochloride salt composition. In another aliquot of 2 mL of the filtrate solution, 16-18 mL of isopropyl alcohol was added to the concentrated oxycodone hydrochloride solution followed by crystallization and drying. The procedure afforded oxycodone hydrochloride salt containing about 6.8 ppm 14-hydroxycodeinone.

Example 6

Analysis of Sample to Determine 14-Hydroxycodeinone and Codeinone

The products of Examples 1-3 were analyzed by the following alternative method to determine the amount of codeinone and 14-hydroxycodeinone present. This method uses a Waters Symmetry C_{18} column maintained at 40° C. with isocratic elution using a mobile phase of sodium phosphate buffer, sodium dodecyl sulfate (SDS), acetonitrile (ACN), and methanol (MeOH).

The reagents used were as follows:

1. Water, HPLC grade or equivalent;
2. Phosphoric acid, 85%, HPLC reagent grade or equivalent;
3. Sodium phosphate monobasic, monohydrate, Enzyme grade or equivalent;
4. Sodium dodecyl sulfate (99%+), Ultrapure, Fluka or equivalent;
5. Acetonitrile, HPLC grade or equivalent;
6. Methanol, HPLC grade or equivalent;
7. Sodium hydroxide, ACS reagent grade or equivalent;
8. Oxycodone HCl with low ABUK to be used as part of the matrix in standard preparation;
9. Codeinone reference material from Rhodes Technologies or equivalent;
10. 14-Hydroxycodeinone reference material from Albany Molecular Research or equivalent

The equipment used was as follows:

A. HPLC System

For this analysis, an HPLC system with a dual wavelength detector was used that was able to operate under isocratic conditions at a flow rate of 0.7 mL per minute with UV detection @ 220 nm, and a column temperature of 40° C.

B. Mobile Phase Filtration System

For this analysis, an HPLC vacuum filtration apparatus with a nylon membrane filter (0.45 μm) was used.

Solutions

i. 50% Sodium Hydroxide Solution (w/v)

50 g of sodium hydroxide pellets were weighed and transferred into a 100-mL volumetric flask. 60-mL of water was then added and sonicated until the pellets were completely dissolved. The pellets were diluted to volume with water and mixed well. (Commercially available 50% w/v NaOH solution may also be used.)

ii. Phosphoric Acid Solution I (~8.5% H_3PO_4)

10 ml of concentrated phosphoric acid (85%) was transferred into a 100 ml volumetric flask containing approximately 50 ml of water. The volume was diluted with water and then mixed.

iii. Phosphoric Acid Solution II (~0.85% H3PO4)

10-mL of 85% phosphoric acid was pipetted into a 1000-mL volumetric flask, diluted to volume with water and mixed well. This was the diluent for the sample and standard preparation.

iv. Mobile Phase

3.45 g±0.1 g of sodium phosphate monobasic monohydrate was weighed into a 1-L flask. 1000 mL of water was added and then stirred with a magnetic stirrer until dissolved. 5.41 g±0.1 g of sodium dodecyl sulfate was added and mixed well until dissolved. This solution was filtered using vacuum filtration with a 0.45-μm nylon membrane filter. The pH of this solution was adjusted with 50% NaOH solution to a final pH of 7.50±0.05.

722.5 ml of the above solution was then mixed with 157.5 mL of acetonitrile, then 120 mL of methanol was added to the solutions and mixed well. The final pH was adjusted to 7.80±0.01 with ~8.5% phosphoric acid solution. The mobile phase was sonicated for about 5 minutes to remove dissolved air.

i. Standard Solution Preparation Calculated Relative to Dried Samples

A. Codeinone/14-Hydroxycodeinone Stock Solution I

25±1 mg of both codeinone and 14-hydroxycodeinone reference materials were weighed and transferred into a 100-mL volumetric flask, diluted to volume and dissolved with ~0.85% phosphoric acid solution II.

ii. 100 ppm Stock Standard II

1-ml of stock solution I was pipetted into a 50-ml volumetric flask, diluted to volume with ~0.85% phosphoric acid solution II and then mixed.

iii. 10 ppm Working Standard III

500±5 mg of Oxycodone low ABUK material was weighed into a 10-ml volumetric flask. 1-ml of stock standard II was pipetted and diluted to volume with ~0.85% phosphoric acid solution II and mixed.

iv. Unspiked Oxycodone Solution

500±5 mg of Oxycodone low ABUK material was weighed into a 10-ml volumetric flask, diluted to volume with ~0.85% phosphoric acid solution II and mixed. (This solution was used to calculate the residual content of both Codeinone and 14-Hydroxycodeinone in the working standard).

E. Resolution Test Mixture (RTM)

1.0-ml of the Codeinone/14-Hydroxycodeinone stock solution I was pipetted into a 50-ml volumetric flask. Using a micropipette, 100 μl of the unspiked Oxycodone solution was transferred and diluted to volume with ~0.85% phosphoric acid solution II. The concentration of Codeinone, 14-Hydroxycodeinone, and Oxycodone was approximately 100 ppm.

F. Sample Preparations

i. 50 mg/mL Oxycodone HCl Sample Solution

500±5 mg of Oxycodone HCl was weighed, in duplicate, into separate 10-mL volumetric flasks for each of Examples 1, 2 and 3. The Oxycodone HCl was then diluted to volume with the ~0.85% phosphoric acid solution II and swirled to dissolve the sample. A sufficient amount of this sample was transferred to an HPLC vial for injection.

G. HPLC Conditions

The HPLC conditions were set as follows:

TABLE 4

HPLC Conditions

Parameter	Condition
HPLC Column	Symmetry C_{18}, 3.0 × 150 mm, 3.5 μm particle size
Mobile Phase	18 mM phosphate/13 mM SDS pH = 7.50:ACN:MeOH (72.25:15.75:12.0) pH = 7.80 ± 0.01
Flow Rate*	0.7 mL/min
Column Temperature	40° C.
Detection	220 nm
Injection Volume	5 μL
Run Time	50 minutes

*Parameter may be adjusted to achieve retention times.

H. System Suitability

One injection (5-μL) of a blank solution (~0.85% phosphoric acid solution II) was made, followed by one injection of the RTM to determine if there was any interfering peaks in the blank solution. 6 injections of the working standard III were made. The system suitability injections were then tested to verify that they met the system suitability criteria as shown in Table 2.

TABLE 5

System Suitability Criteria

Parameter	Acceptance Criteria
Resolution between Codeinone and 14-Hydroxycodeinone	NLT 8
Resolution between 14-Hydroxycodeinone and Oxycodone	NLT 2
Tailing factor for Oxycodone	0.7-2.0
Relative retention times for Codeinone based on Oxycodone	Approx. 0.44
Relative retention times for 14-Hydroxycodeinone based on Oxycodone	Approx. 0.85
% RSD of 6 system suitability injections for Codeinone and 14-Hydroxycodeinone	NMT 20%

The expected retention times were as follows:

Components	Expected Retention Times
Codeinone	14 ± 2 min
14-Hydroxycodeinone	27 ± 4 min
Oxycodone	32 ± 6 min

I. Injection Procedure

Once the column was equilibrated, the sample and standard solutions were injected according to the following sequence of Table 3:

TABLE 6

Blank (diluent)	1 injection
Resolution solution	1 injection
Working Standard III	6 injections for RSD, last 2 injections for calibration
Blank (diluent)	2 injections
Unspiked Oxycodone solution	2 injections
Sample 1 Prep# 1	2 injections
Working Standard III	2 injections
Sample 1 Prep# 2	2 injections
Sample 2 Prep# 1	2 injections
Sample 2 Prep# 2	2 injections
Working Standard III	2 injections
Sample 3, Prep# 1	2 injections
Sample 3, Prep# 2	2 injections
Working Standard III	2 injections

The Codeinone and 14-Hydroxycodeinone peaks were identified using the relative retention times as discussed above.

Calculations

The responses of Codeinone and 14-Hydroxycodeinone peaks were measured and recorded. The content of Codeinone and 14-Hydroxycodeinone was calculated in ppm using the following equation:

$$ppm = \frac{Rs \times Wstd}{Rstd \times Ws} \times \frac{1}{100} \times \frac{1}{50} \times \frac{1}{10} \times \frac{10}{1} \times \frac{1{,}000{,}000}{1}$$

$$ppm = \frac{Rs \times Wstd \times 200}{Rstd \times Ws}$$

Where:

ppm=Parts per millions of codeinone or 14-Hydroxycodeinone in Oxycodone HCl

Rs=Response of Codeinone or 14-Hydroxycodeinone in Sample Solution.

Rstd=Response of Codeinone or 14-Hydroxycodeinone in Standard Solution minus the response of unspiked standard

Wstd=Weight of Standard, corrected for purity, mg

Ws=Weight of Sample, mg

1000000=Conversion Factor for ppm

% Codeinone/14-hydroxycodeinone=ppm/10,000

The results for Example 1 utilizing the procedure of Example 6 gave a result of <5 ppm of codeinone and 8 ppm of 14-hydroxycodeinone.

The results for Example 2 utilizing the procedure of Example 6 gave a result of <5 ppm of codeinone and <5 ppm of 14-hydroxycodeinone.

The results for Example 3 utilizing the procedure of Example 6 gave a result of <5 ppm of codeinone and 10 ppm of 14-hydroxycodeinone.

Many other variations of the present invention will be apparent to those skilled in the art and are meant to be within the scope of the claims appended hereto.

What is claimed is:

1. An oral dosage form comprising particles, the particles comprising from about 5 mg to about 320 mg oxycodone hydrochloride active pharmaceutical ingredient having less than 25 ppm 14-hydroxycodeinone, wherein at least a portion of the 14-hydroxycodeinone is derived from 8α,14-dihydroxy-7,8-dihydrocodeinone during conversion of oxycodone free base to oxycodone hydrochloride, said particles being coated with an amount of hydrophobic material effective to provide a sustained release of the oxycodone hydrochloride when the coated particles are exposed to an aqueous solution.

2. An oral dosage form comprising (i) from about 5 mg to about 320 mg of oxycodone hydrochloride active pharmaceutical ingredient having less than 25 ppm 14-hydroxyco-

deinone, wherein at least a portion of the 14-hydroxycodeinone is derived from 8α,14-dihydroxy-7,8-dihydrocodeinone during conversion of oxycodone free base to oxycodone hydrochloride; and (ii) a sustained release material, wherein the sustained release material is film coated onto said oxycodone hydrochloride active pharmaceutical ingredient.

3. An oral dosage form comprising: (i) from about 5 mg to about 320 mg of oxycodone hydrochloride active pharmaceutical ingredient having less than 25 ppm 14-hydroxycodeinone, wherein at least a portion of the 14-hydroxycodeinone is derived from 8α,14-dihydroxy-7,8-dihydrocodeinone during conversion of oxycodone free base to oxycodone hydrochloride; and (ii) a pharmaceutically acceptable excipient.

4. The oral dosage form of claim **1**, wherein the 14-hydroxycodeinone is derived solely from 8α,14-dihydroxy-7,8-dihydrocodeinone.

5. The oral dosage form of claim **2**, wherein the 14-hydroxycodeinone is derived solely from 8α,14-dihydroxy-7,8-dihydrocodeinone.

6. The oral dosage form of claim **3**, wherein the oxycodone hydrochloride active pharmaceutical ingredient has a lower limit of the 14-hydroxycodeinone of 0.25 ppm, 0.5 ppm, 1 ppm, 2 ppm or 5 ppm.

7. The oral dosage form of claim **3**, wherein the 14-hydroxycodeinone is derived solely from 8α,14-dihydroxy-7,8-dihydrocodeinone.

8. The oral dosage form of claim **1**, wherein the oxycodone hydrochloride active pharmaceutical ingredient has a lower limit of the 14-hydroxycodeinone of 0.25 ppm, 0.5 ppm, 1 ppm, 2 ppm or 5 ppm.

9. The oral dosage form of claim **2**, wherein the oxycodone hydrochloride active pharmaceutical ingredient has a lower limit of the 14-hydroxycodeinone is of 0.25 ppm, 0.5 ppm, 1 ppm, 2 ppm or 5 ppm.

10. The oral dosage form of claim **8**, which is a tablet or a capsule.

11. The oral dosage form of claim **8** comprising about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 80 mg, about 100 mg, about 160 mg or about 320 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

12. The oral dosage form of claim **8**, comprising 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg or 160 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

13. The oral dosage form of claim **9**, which is a tablet or a capsule.

14. The oral dosage form of claim **9** comprising about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 80 mg, about 100 mg, about 160 mg or about 320 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

15. The oral dosage form of claim **9** comprising 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg or 160 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

16. The oral dosage form of claim **6**, which is a tablet or a capsule.

17. The oral dosage form of claim **6** comprising about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 80 mg, about 100 mg, about 160 mg or about 320 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

18. The oral dosage form of claim **6** comprising 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg or 160 mg of the oxycodone hydrochloride active pharmaceutical ingredient.

19. The oral dosage form of claim **3**, wherein the pharmaceutically acceptable excipient comprises a sustained release carrier.

* * * * *

EXHIBIT B

US007674800B2

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

(10) **Patent No.: US 7,674,800 B2**
(45) **Date of Patent: *Mar. 9, 2010**

(54) **OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE**

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This patent is subject to a terminal disclaimer.

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

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

See application file for complete search history.

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(57) **ABSTRACT**

In certain embodiments the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm of 14-hydroxycodeinone.

81 Claims, 5 Drawing Sheets

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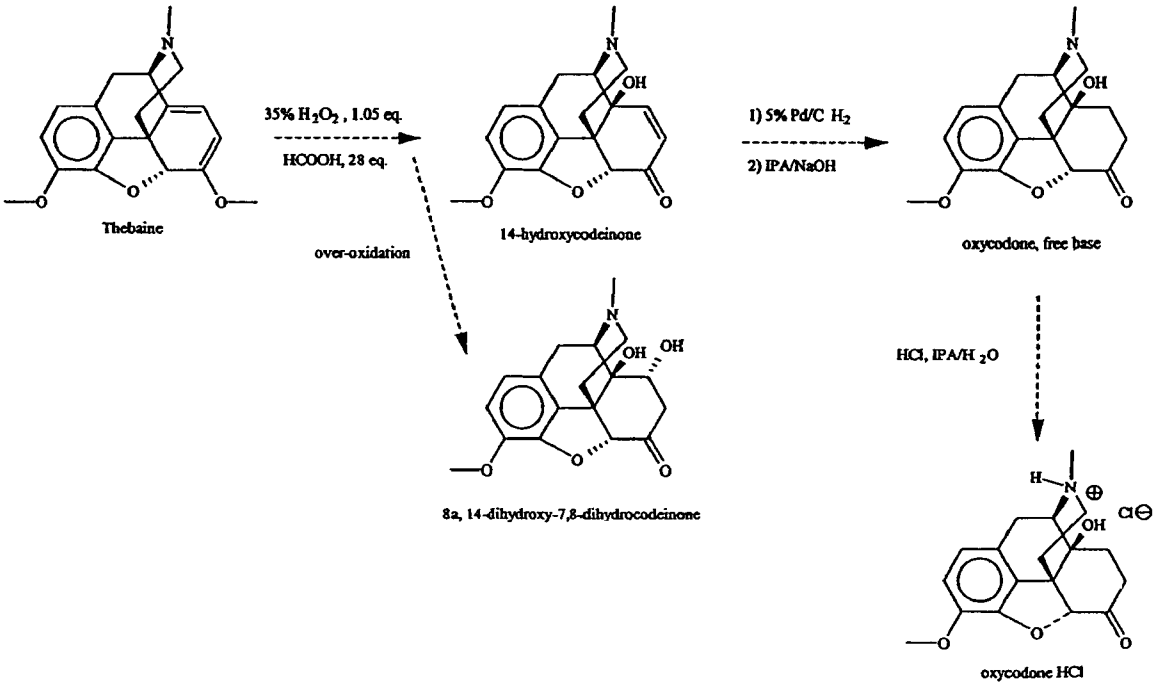
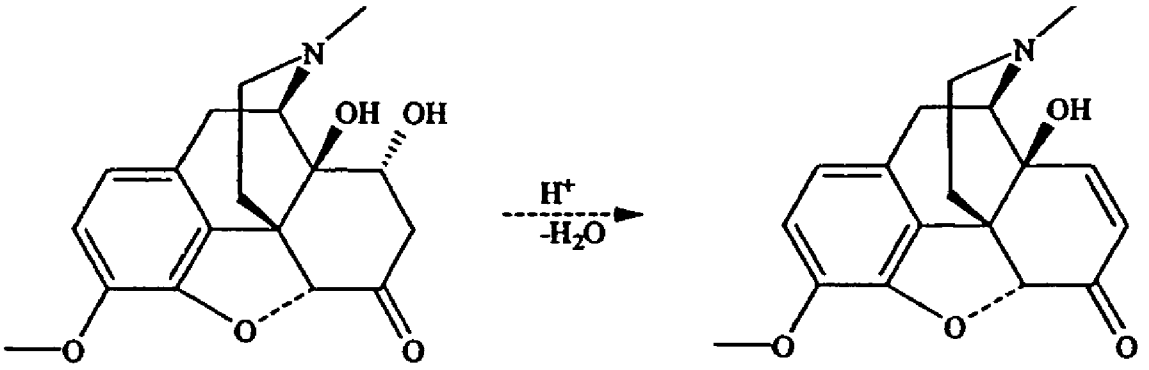
FIGURE 1



Reaction scheme of the process used to produce oxycodone HCl from thebaine.

FIGURE 2



8a,14-dihydroxy-7,8-dihydrocodeinone

14-hydroxycodeinone

Dehydration of 8α, 14-dihydroxy-7,8-dihydrocodeinone

FIGURE 3

Typical HPLC Chromatogram of RTM Solution

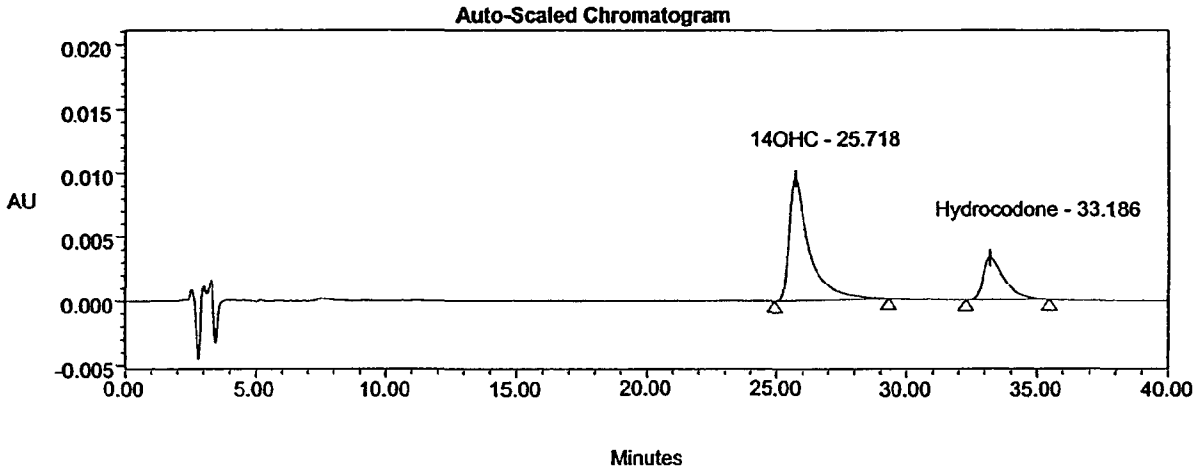


Figure 4

Typical HPLC Chromatogram of the Working 100 PPM 14OHC Standard Solution

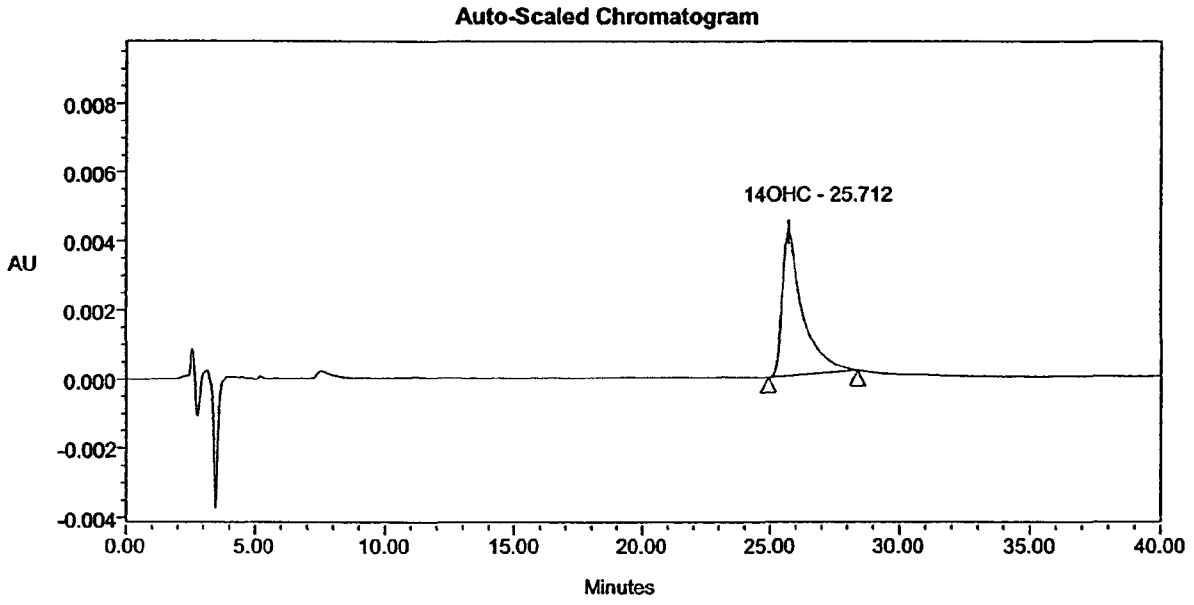
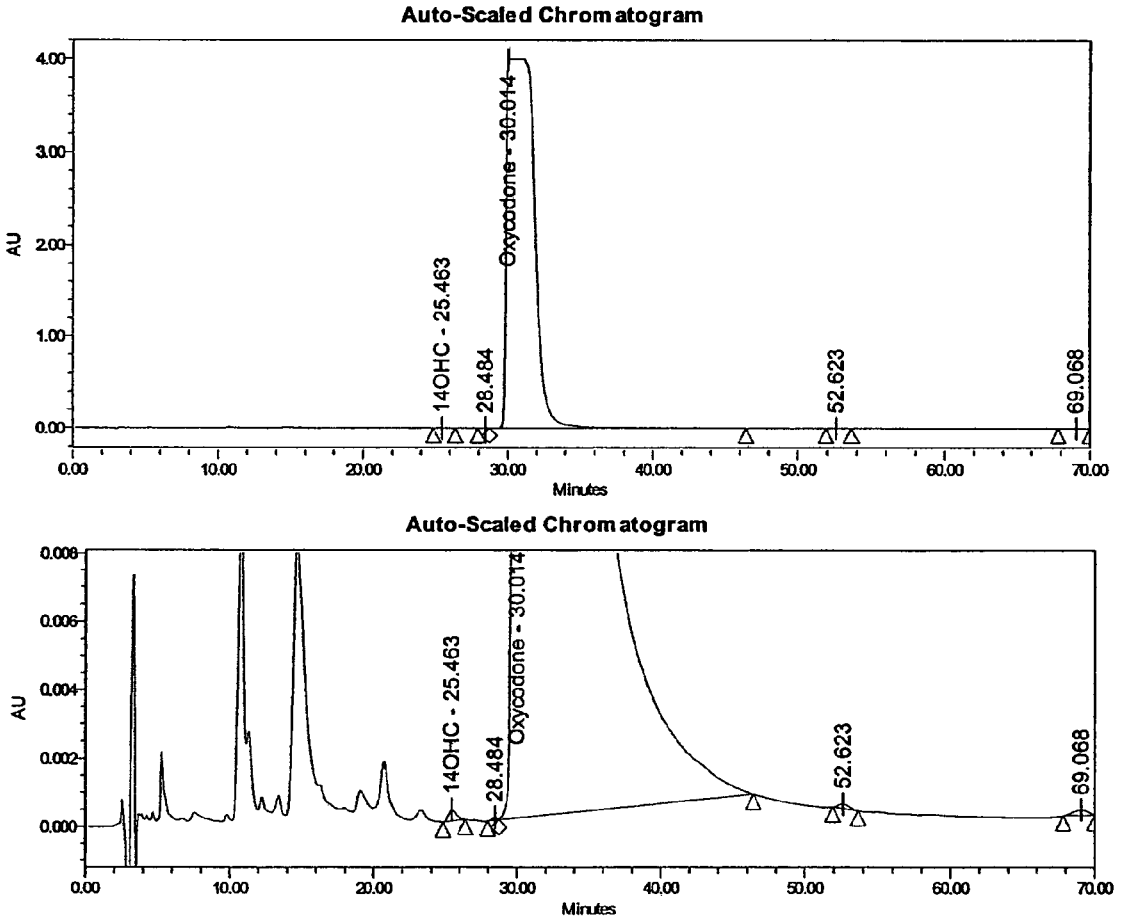


FIGURE 5

Typical HPLC Chromatogram of the Sample Solution containing Oxycodone API



OXYCODONE HYDROCHLORIDE HAVING LESS THAN 25 PPM 14-HYDROXYCODEINONE

This application is a continuation of U.S. patent application Ser. No. 11/391,897, filed Mar. 29, 2006, which is a continuation of U.S. patent application Ser. No. 11/093,626, filed Mar. 30, 2005, now U.S. Pat. No. 7,129,248, which claims priority to U.S. Provisional Application No. 60/651,778, filed Feb. 10, 2005, U.S. Provisional Application No. 60/648,625, filed Jan. 31, 2005, U.S. Provisional Application No. 60/620,072, filed Oct. 18, 2004, U.S. Provisional Application No. 60/601,534, filed Aug. 13, 2004, and U.S. Provisional Application No. 60/557,492, filed Mar. 30, 2004, all of which are hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to a process for reducing the amount of 14-hydroxycodeinone in an oxycodone hydrochloride preparation.

BACKGROUND OF THE INVENTION

Oxycodone is a semi-synthetic opioid analgesic that exerts an agonist effect at specific, saturable opioid receptors in the CNS and other tissues. In man, oxycodone may produce any of a variety of effects including analgesia.

Purdue Pharma L.P currently sells sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the trade name OxyContin®.

U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912; and 5,656,295 disclose sustained release oxycodone formulations.

Thebaine, a compound derived from opium, although having no medicinal use in itself, is useful as a starting material in synthetic schemes for the production of oxycodone. In other schemes, codeine can be utilized as the starting material for the production of oxycodone. 14-hydroxycodeinone is the immediate precursor to oxycodone in these schemes.

Methods of producing thebaine or 14-hydroxy substituted opium derivatives have been reported, e.g. in U.S. Pat. No. 3,894,026 and U.S. Pat. No. 4,045,440.

The oxidation of codeine to codeinone, an initial step in the synthesis of opium derivatives has been reported in EP 0889045, U.S. Pat. No. 6,008,355 and in the J. Am. Chem. Soc., 1051, 73, 4001 (Findlay).

The reaction of codeinone to 14-hydroxycodeinone has been reported in U.S. Pat. No. 6,008,355 and in Tetrahedron 55, 1999 (Coop and Rice).

The methylation of codeinone to thebaine has been reported in Heterocycles, 1988, 49, 43-7 (Rice) and EP0889045.

U.S. Pat. No. 6,177,567 describes the hydrogenation of 14-hydroxycodeinone to oxycodone by reduction with diphenylsilane and Pd(Ph3P)/ZnCl2 or with sodium hypophosphite in conjunction with a Pd/C catalyst in aqueous acetic acid.

Krabnig et al. in "Optimization of the Synthesis of Oxycodone and 5-Methyloxycodone" Arch. Pharm. (1996), 329 (6), (325-326) describes hydrogenating a solution of 14-hydroxycodeinone in glacial acetic acid with a Pd—C-catalyst at 30 psi at the described conditions.

During the oxidation of thebaine to give 14-hydroxycodeinone, several overoxidized products are formed including 8,14-dihydroxy-7,8-dihydrocodeinone. In the production of oxycodone free base from the 14-hydroxycodeinone, the 8,14-dihydroxy-7,8-dihydrocodeinone is carried though the process. During conversion of the oxycodone free base to oxycodone hydrochloride, the impurity undergoes acid-catalyzed dehydration and is converted into 14-hydroxycodeinone. Thus, 14-hydroxycodeinone is present in the final oxycodone hydrochloride composition. Oxycodone hydrochloride API (active pharmaceutical ingredient) is available from a variety of manufacturers such as Johnson Matthey and Mallinckrodt. Current commercially-available oxycodone hydrochloride API, and oxycodone hydrochloride prepared by known procedures, have a level of 14-hydroxycodeinone of greater than 100 ppm.

There is a continuing need in the art to provide an oxycodone hydrochloride composition that contains reduced amounts of 14-hydroxycodeinone as compared to compositions known in the art.

All references cited herein are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of certain embodiments of the present invention to provide a process for reducing the 14-hydroxycodeinone in an oxycodone hydrochloride composition to an amount of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is an object of certain embodiments of the present invention to provide a process for reacting an oxycodone base composition with hydrochloric acid under conditions to produce an oxycodone hydrochloride composition having an amount of 14-hydroxycodeinone of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is a further object of certain embodiments of the present invention to provide an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

It is a further object of certain embodiments of the present invention to provide a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm by reacting an oxycodone base composition with hydrochloric acid under conditions suitable to promote dehydration of 8,14-dihydroxy-7,8-dihydrocodeinone to 14-hydroxycodeinone during salt formation and under reducing conditions so as to convert the 14-hydroxycodeinone to oxycodone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising reacting an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of more than 100 ppm under conditions that reduce the amount of 14-hydroxycodeinone to a level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments, the invention is directed to an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising subjecting an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of greater than 100 ppm to hydrogenation to an extent that the amount of 14-hydroxycodeinone in the composition is reduced to an

amount of less than less 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm.

In certain embodiments disclosed herein, the oxycodone composition having a 14-hydroxycodeinone level of less than 25 ppm can be subsequently hydrogenated to further decrease the amount of 14-hydroxycodeinone, e.g., from about 15 ppm to about 10 ppm or less.

In one embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of 100 ppm or higher, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm. In another embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of between 15 ppm and 25 ppm, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than about 10 ppm, or less than about 5 ppm. In another embodiment, where the starting material is an oxycodone hydrochloride composition comprising 14-hydroxycodeinone in an amount of between 10 ppm and 25 ppm, the final oxycodone hydrochloride composition has a 14-hydroxycodeinone level of less than about 5 ppm.

In certain embodiments of the present invention, the process for preparing the oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprises hydrogenating the starting material under reflux. In certain embodiments, the process further comprises recovering the resultant oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm comprising hydrogenating under reflux, a starting oxycodone hydrochloride composition having a 14-hydroxycodeinone level of greater than 100 ppm in a suitable solvent for a time sufficient to produce an oxycodone composition having a 14-hydroxycodeinone level of less than 25 ppm, less than about 15 ppm, less than about 10 ppm, or less than about 5 ppm; and recovering the oxycodone hydrochloride composition having a 14-hydroxycodeinone level of less than 25 ppm by crystallization and removal from the solvent (e.g., by filtration).

In certain embodiments, the oxycodone hydrochloride composition of the present invention has a lower limit of 0.25 ppm, 0.5 ppm, 1 ppm, 2 ppm or 5 ppm of 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising reacting in a suitable solvent an oxycodone base composition with hydrochloric acid in an amount greater than 1.0 molar equivalent as compared to the oxycodone base composition, the reacting step being performed under reducing conditions, to form an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising hydrogenating a 14-hydroxycodeinone composition to obtain an oxycodone free base composition; converting the oxycodone free base composition to oxycodone hydrochloride; and hydrogenating the oxycodone hydrochloride to obtain an oxycodone composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising hydrogenating a 14-hydroxycodeinone composition to obtain an oxycodone free base composition; converting the oxycodone free base composition to oxycodone hydrochloride; isolating the oxycodone hydrochloride; and hydrogenating the oxycodone hydrochloride to obtain an oxycodone composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone comprising oxidizing a thebaine composition to form 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition; hydrogenating the 14-hydroxycodeinone composition to form an oxycodone base composition; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing 14-hydroxycodeinone comprising oxidizing a thebaine composition to form 14-hydroxycodeinone composition, the oxidizing being performed at a suitable pH to minimize or eliminate the production of 8,14-dihydroxy-7,8-dihydrocodeinone in the 14-hydroxycodeinone composition;

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising reacting an oxycodone base composition with an acid having a higher pH than hydrochloric acid to form a corresponding acid addition salt of oxycodone, and converting the acid addition salt of oxycodone to oxycodone hydrochloride.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising contacting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone with a substance that preferentially removes the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising subjecting an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone to chromatographic separation to preferentially removes the 8,14-dihydroxy-7,8-dihydrocodeinone as compared to the oxycodone base; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition having a 14-hydroxycodeinone level in an amount of less than 25 ppm comprising reacting in a suitable solvent an oxycodone base composition having an amount of 8,14-dihydroxy-7,8-dihydrocodeinone, with boronated polystyrene resin; and converting the oxycodone base composition to an oxycodone hydrochloride composition having less than 25 ppm 14-hydroxycodeinone.

In certain embodiments, the invention is directed to a process for preparing an oxycodone hydrochloride composition comprising reacting in a suitable solvent an oxycodone base