OXYCODONE COMPOSITIONS

This application is a continuation of U.S. patent application Ser. No. 13/366,755, filed on Feb. 6, 2012, which is a continuation of U.S. patent application Ser. No. 12/893,681, filed on Sep. 29, 2010, which is a continuation of U.S. patent application Ser. No. 12/380,800, filed Mar. 4, 2009, which is a continuation of U.S. patent application Ser. No. 11/653,529, filed Jan. 16, 2007, which 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 LP 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.