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(12) **United States Patent**
Wright et al.(10) **Patent No.:** **US 9,034,376 B2**
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(2013.01); **A61K 31/192** (2013.01); **A61K**
9/1652 (2013.01); **A61K 47/26** (2013.01)(71) Applicants: **Purdue Pharma L.P.**, Stamford, CT
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Pharmaceuticals L.P., Wilson, NC (US)(58) **Field of Classification Search**
None
See application file for complete search history.(72) Inventors: **Curtis Wright**, Rockport, MA (US);
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4,200,098 A 4/1980 Ayer et al.(*) Notice: Subject to any disclaimer, the term of this
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U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-
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A61K 47/26 (2006.01)(52) **U.S. Cl.**CPC **A61K 31/167** (2013.01); **A61K 9/2013**
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Primary Examiner — Robert A Wax*Assistant Examiner* — Olga V Tcherkasskaya(74) *Attorney, Agent, or Firm* — Lowenstein Sandler LLP(57) **ABSTRACT**Disclosed in certain embodiments is a controlled release oral
dosage form comprising a therapeutically effective amount of
a drug susceptible to abuse together with one or more phar-
maceutically acceptable excipients; the dosage form further
including a gelling agent in an effective amount to impart a
viscosity unsuitable for administration selected from the
group consisting of parenteral and nasal administration to a
solubilized mixture formed when the dosage form is crushed
and mixed with from about 0.5 to about 10 ml of an aqueous
liquid; the dosage form providing a therapeutic effect for at
least about 12 hours when orally administered to a human
patient.**19 Claims, No Drawings**

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**PHARMACEUTICAL FORMULATION
CONTAINING GELLING AGENT**

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/255,502, filed Apr. 17, 2014, which is a continuation of U.S. patent application Ser. No. 13/726,324, filed Dec. 24, 2012, which is a continuation of U.S. patent application Ser. No. 13/349,449, filed Jan. 12, 2012, now issued as U.S. Pat. No. 8,337,888, which is a continuation of U.S. patent application Ser. No. 12/653,115, filed Dec. 8, 2009, which is a continuation of U.S. patent application Ser. No. 10/214,412, filed Aug. 6, 2002, which claims the benefit of U.S. Provisional Application No. 60/310,534, filed Aug. 6, 2001. The contents of these applications are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high." Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for immediate release upon oral or nasal administration. An opioid formulation can also be abusable by administration of more than the prescribed dose of the drug.

Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin®Nx from Sanofi-Winthrop. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978 (Valoron®N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain.

Purdue Pharma EP currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the tradename OxyContin.

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

U.S. Pat. Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

U.S. Pat. No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms.

WO 99/32119 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms.

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U.S. Pat. No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

U.S. Pat. No. 3,980,766 to Shaw et al., is related to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet form of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies.

All documents cited herein, including the foregoing, 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 invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

It is a further object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less abuse potential.

These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; and at least one aversive agent for reducing the abuse of the opioid analgesic.

In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; and an aversive agent or agents as a component(s) of the dosage form helps to prevent injection, inhalation, and/or oral abuse by decreasing the "attractiveness" of the dosage form to a potential abuser.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a bittering agent to discourage an abuser from tampering with the dosage form and thereafter inhaling or swallowing the tampered dosage form. Preferably, the bittering agent is released when the dosage form is tampered with and provides an unpleasant taste to the abuser upon inhalation and/or swallowing of the tampered dosage form.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as an irritant to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the irritant is released when the dosage form is tampered with and provides a burning or irritating effect to the abuser upon inhalation, injection, and/or swallowing of the tampered dosage form.

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