



US008835459B2

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

(10) **Patent No.:** **US 8,835,459 B2**
(45) **Date of Patent:** ***Sep. 16, 2014**

- (54) **SUBLINGUAL FENTANYL SPRAY** 2002/0055496 A1 5/2002 McCoy et al.
- 2002/0160991 A1 10/2002 Shao
- (71) Applicant: **Insys Therapeutics, Inc.**, Phoenix, AZ 2003/0039680 A1 2/2003 Dugger, III
(US) 2003/0077228 A1 4/2003 Dugger, III
2003/0077229 A1 4/2003 Dugger, III
2003/0082107 A1 5/2003 Dugger, III
2003/0095925 A1 5/2003 Dugger, III
(72) Inventors: **S. George Kottayil**, Long Grove, IL 2003/0095926 A1 5/2003 Dugger, III
(US); **Venkat R. Goskonda**, Phoenix, 2003/0095927 A1 5/2003 Dugger, III
AZ (US); **Zhongyuan Zhu**, Vernon 2003/0190286 A1 10/2003 Dugger, III
Hills, IL (US); **Linet Kattookaran**, 2003/0190290 A1 * 10/2003 Ross 424/45
Mount Prospect, IL (US); **Neha Parikh**, 2004/0092428 A1 5/2004 Chen et al.
Chicago, IL (US) 2004/0120895 A1 6/2004 Dugger, III
2004/0136913 A1 7/2004 Dugger, III et al.
(73) Assignee: **Insys Therapeutics, Inc.**, Phoenix, AZ 2004/0136914 A1 7/2004 Dugger, III et al.
(US) 2004/0136915 A1 7/2004 Dugger, III et al.
2004/0141923 A1 7/2004 Dugger, III et al.
(*) Notice: Subject to any disclaimer, the term of this 2004/0265239 A1 12/2004 Dugger, III et al.
patent is extended or adjusted under 35 2005/0002867 A1 1/2005 Dugger, III et al.
U.S.C. 154(b) by 0 days. 2005/0163719 A1 7/2005 Dugger, III et al.
This patent is subject to a terminal dis- 2005/0180923 A1 8/2005 Dugger, III et al.
claimer. 2005/0281752 A1 12/2005 Dugger, III
2005/0281753 A1 12/2005 Dugger, III
2005/0287075 A1 12/2005 Dugger, III
2006/0062812 A1 3/2006 Ross et al.
(21) Appl. No.: **13/895,111** 2007/0071806 A1 * 3/2007 McCarty 424/451
2007/0261695 A1 11/2007 Kottayil et al.
(22) Filed: **May 15, 2013** 2009/0124554 A1 5/2009 Dugger, III
2009/0162300 A1 6/2009 Dugger, III
2012/0035216 A1 * 2/2012 Palmer et al. 514/326

(65) **Prior Publication Data**
US 2013/0296368 A1 Nov. 7, 2013

Related U.S. Application Data
(63) Continuation of application No. 12/221,333, filed on Aug. 1, 2008, now Pat. No. 8,486,973.
(60) Provisional application No. 60/963,076, filed on Aug. 2, 2007, provisional application No. 60/963,253, filed on Aug. 3, 2007.

(51) **Int. Cl.**
A01N 43/40 (2006.01)
A61K 31/445 (2006.01)
A61M 11/00 (2006.01)
A61K 31/435 (2006.01)
A61K 31/4468 (2006.01)
A61K 9/00 (2006.01)
(52) **U.S. Cl.**
CPC *A61K 31/4468* (2013.01); *A61K 31/435* (2013.01); *A61M 11/00* (2013.01); *A61K 31/445* (2013.01); *A61K 9/006* (2013.01); *A61K 9/0056* (2013.01)
USPC **514/329**; 128/200.14

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**
U.S. PATENT DOCUMENTS
4,244,478 A 1/1981 Handman
5,219,083 A 6/1993 Liebert et al.
5,958,379 A 9/1999 Regenold et al.
5,976,504 A 11/1999 Russell
6,759,059 B1 7/2004 Pettersson et al.
6,946,150 B2 9/2005 Whittle
8,486,972 B2 7/2013 Kottayil et al.

FOREIGN PATENT DOCUMENTS

RU	2156126	9/2000
RU	2232580	7/2004
WO	WO 90/07333	7/1990
WO	WO 00/47203	8/2000
WO	WO 01/97780 A2	12/2001
WO	WO 2004/016243 A2	2/2004
WO	WO 2004/080382	9/2004
WO	WO 2004/075877	10/2004
WO	WO 2007-007059	1/2007
WO	WO 2007/087431	8/2007

OTHER PUBLICATIONS

Int'l Preliminary Report on Patentability from related Int'l Application No. PCT/US08/09359 dated Feb. 2, 2010.
Lejus, et al., "Fentanyl versus sufentanil: plasma concentrations during continuous epidural postoperative infusion in children," British Journal of Anaesthesia, vol. 85, Issue 4, Oct. 2000, pp. 615-617.
Examination Report for corresponding Australian Patent Application No. 2008282743, mailed on Feb. 9, 2011.
Smyth, et al., 2003, AAPS PharmSciTech 2003; 4 (3):1-11.

(Continued)

Primary Examiner — Robert Landsman
(74) *Attorney, Agent, or Firm* — Wood, Phillips, Katz, Clark & Mortimer

(57) **ABSTRACT**

The present invention is directed to sublingual formulations containing fentanyl, a pharmaceutically acceptable salt thereof, or derivative thereof, suitable for administration to a patient, and methods for treatment with the formulations.

6 Claims, 10 Drawing Sheets

(56)

References Cited

OTHER PUBLICATIONS

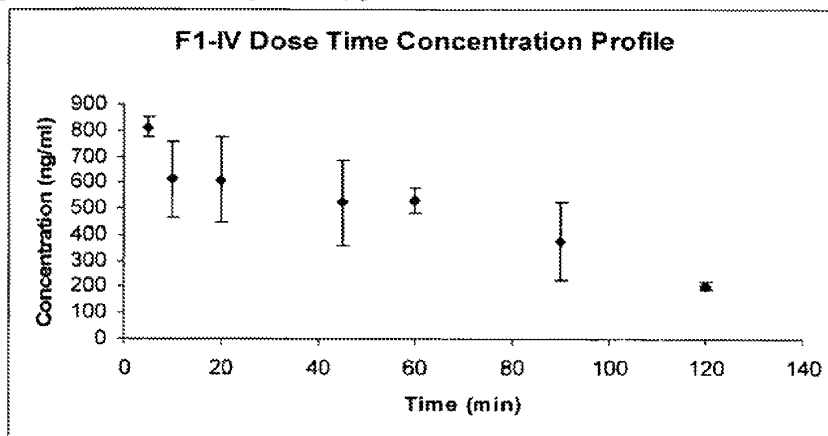
Examination Report for corresponding Australian Patent Application No. 2008282743, mailed on Nov. 1, 2012.
Examination Report for corresponding European Patent Application No. 07762549.9, mailed on Sep. 30, 2010.
Supplementary European Search Report, 2 pages, for corresponding European Patent Application No. 07762549.9, mailed on Sep. 30, 2010.
Office Action on Chinese Patent Application No. 200780003555.X dated Jul. 9, 2010.
International Search Report and Written Opinion, dated Jul. 11, 2008 from corresponding Int'l Application No. PCT/US07/02163.
Mathar, L.E., et al. "Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery" Br. J. Clin. Pharmacol. Jan. 1998, vol. 46, pp. 37-43.

Marier, J-F., et al. "Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation", Br. J. Clin. Pharmacol. Aug. 2006, vol. 63, No. 1, pp. 121-124, esp. p. 123, Figure 1.
International Preliminary Report on Patentability dated Aug. 26, 2008 from corresponding Int'l Application No. PCT/US07/02163.
Examination Report dated Aug. 6, 2009 from corresponding Australian Application No. 2007208229.
Examination Report dated May 5, 2010 from corresponding Canadian Application No. 2,637,672.
Examination Report dated Mar. 18, 2010 from corresponding New Zealand Application No. 569949.
An English translation of the Russian Examination Report dated Aug. 2009 from corresponding Russian Application No. 2008130763.
ISR and Written Opinion from related Int'l Application No. PCT/US08/09359 dated Jan. 9, 2009.

* cited by examiner

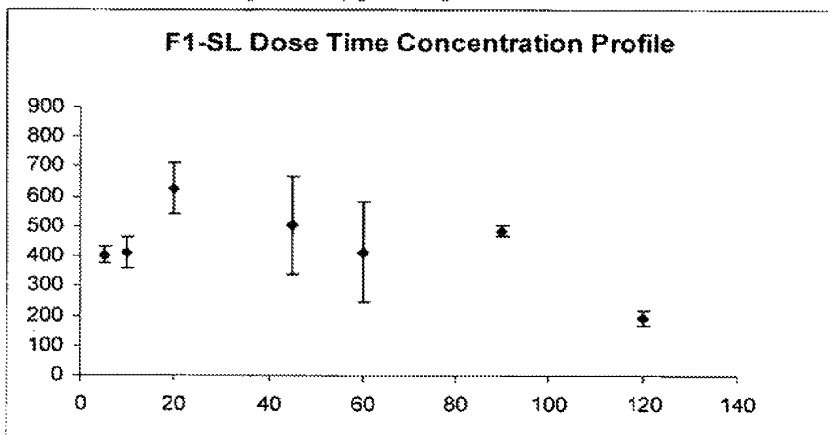
Plasma concentration-time curves after IV & SL doses of Fentanyl

Figure 1: Formula of Example 1, 50 µg IV dose



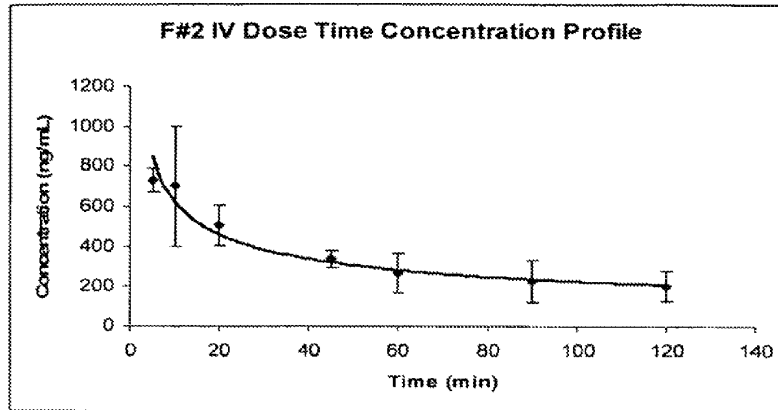
Mean (±S.E.) plasma concentration–time profiles following intravenous administration of Fentanyl (*n*=3).

Figure 2: Formula of Example 1, 50 µg Sublingual dose



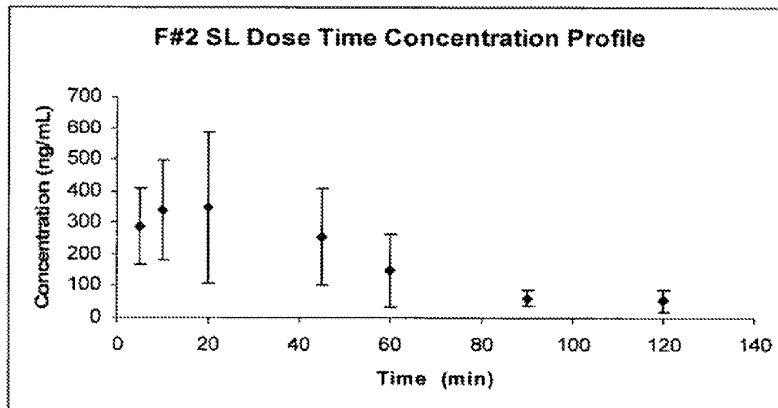
Mean (±S.E.) plasma concentration–time profiles following sublingual administration of Fentanyl (*n*=3)

Figure 3: Formula of Example 2, 80 µg IV dose



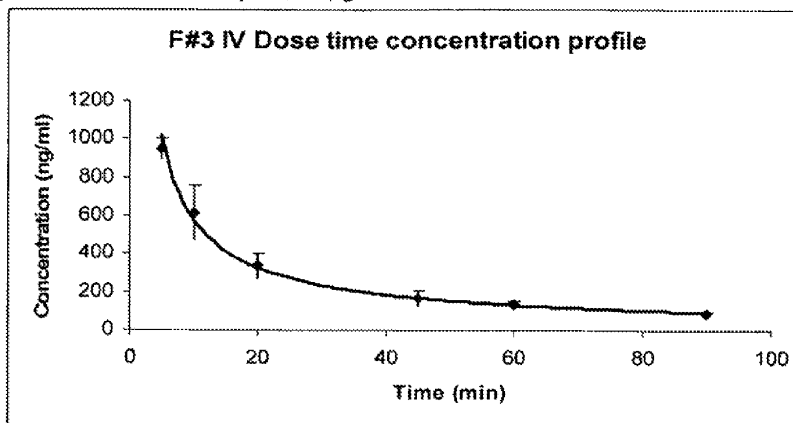
Mean (\pm S.E.) plasma concentration–time profiles following intravenous administration of Fentanyl ($n=3$).

Figure 4: Formula of Example 2, 80 µg SL dose



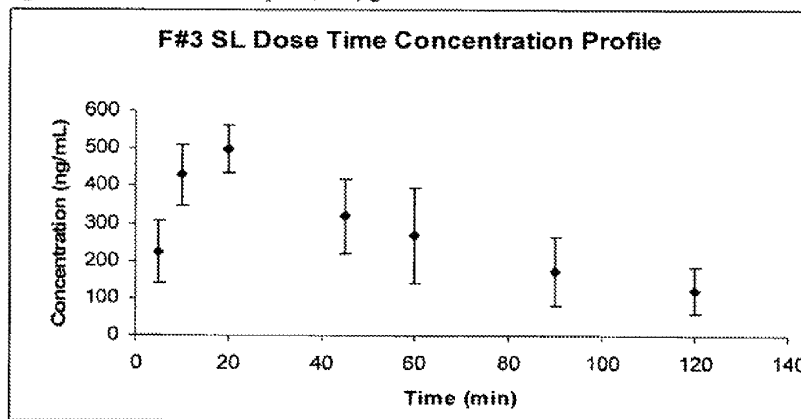
Mean (\pm S.E.) plasma concentration–time profiles following sublingual administration of Fentanyl ($n=3$).

Figure 5: Formula of Example 3, 50 µg IV dose



Mean (\pm S.E.) plasma concentration–time profiles following intravenous administration of Fentanyl ($n=3$)

Figure 6: Formula of Example 3, 50 µg SL dose



Mean (\pm S.E.) plasma concentration–time profiles following sublingual administration of Fentanyl ($n=3$)

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.