US 20150283123A1

(19) **United States**

(12) **Patent Application Publication**

WATTS et al.

(10) **Pub. No.: US 2015/0283123 A1**

(43) **Pub. Date: Oct. 8, 2015**

(54) **INTRANASAL SPRAY DEVICE CONTAINING PHARMACEUTICAL COMPOSITION**

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(21) Appl. No.: **14/747,289**

(22) Filed: **Jun. 23, 2015**

Related U.S. Application Data

(60) Continuation of application No. 13/541,325, filed on Jul. 3, 2012, now Pat. No. 9,078,814, which is a division of application No. 12/047,388, filed on Mar. 13, 2008, now Pat. No. 8,216,604, which is a division of application No. 10/753,628, filed on Jan. 8, 2004, now abandoned.

(30) **Foreign Application Priority Data**

Jan. 10, 2003 (GB) 0300531.1

Publication Classification

(51) **Int. Cl.**

A61K 31/4468	(2006.01)
A61M 15/08	(2006.01)
A61K 47/26	(2006.01)
A61M 11/00	(2006.01)
A61K 47/36	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/4468*** (2013.01); ***A61K 47/36*** (2013.01); ***A61K 9/0043*** (2013.01); ***A61K 47/26*** (2013.01); ***A61M 11/00*** (2013.01); ***A61M 15/08*** (2013.01)

(57) **ABSTRACT**

An intranasal spray device contains a composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof to an animal includes an aqueous solution of fentanyl or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable additive selected from (i) a pectin and (ii) a poloxamer and chitosan or a salt or derivative thereof; provided that when the composition comprises a pectin it is substantially free of divalent metal ions; and which, in comparison to a simple aqueous solution of fentanyl administered intranasally at the same dose, provides a peak plasma concentration of fentanyl (C_{max}) that is from 10 to 80% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose. A method for treating or managing pain by intranasally administering the composition is also disclosed.

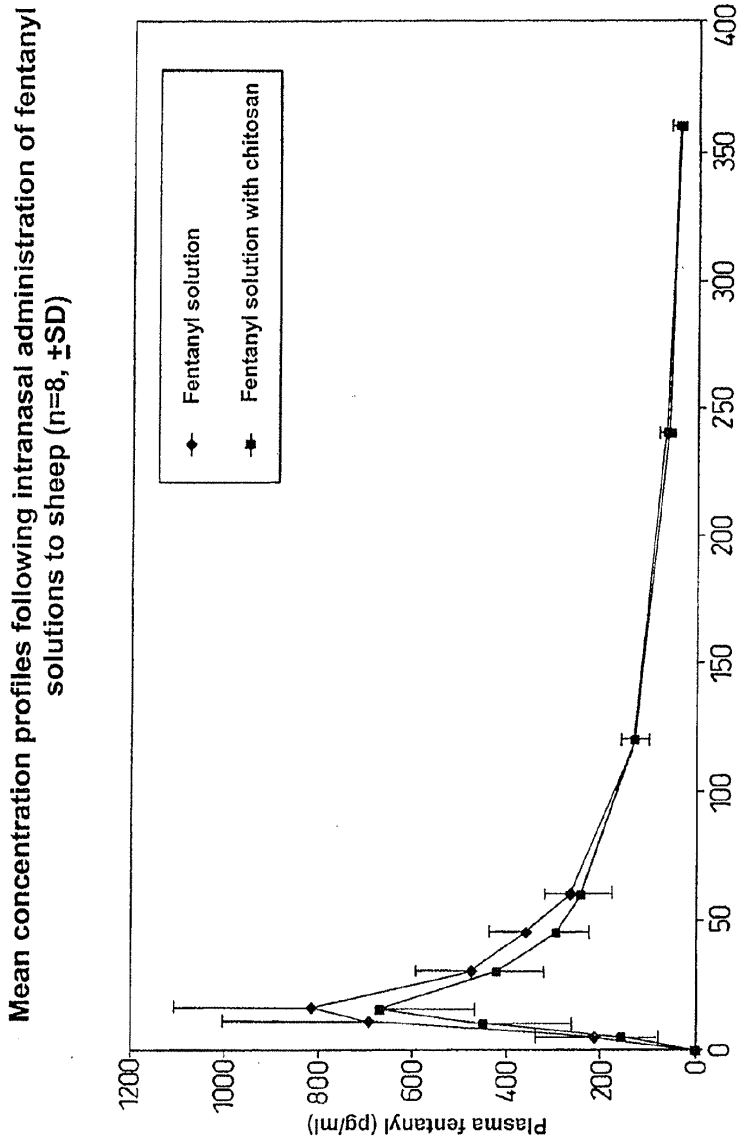

Fig. 1

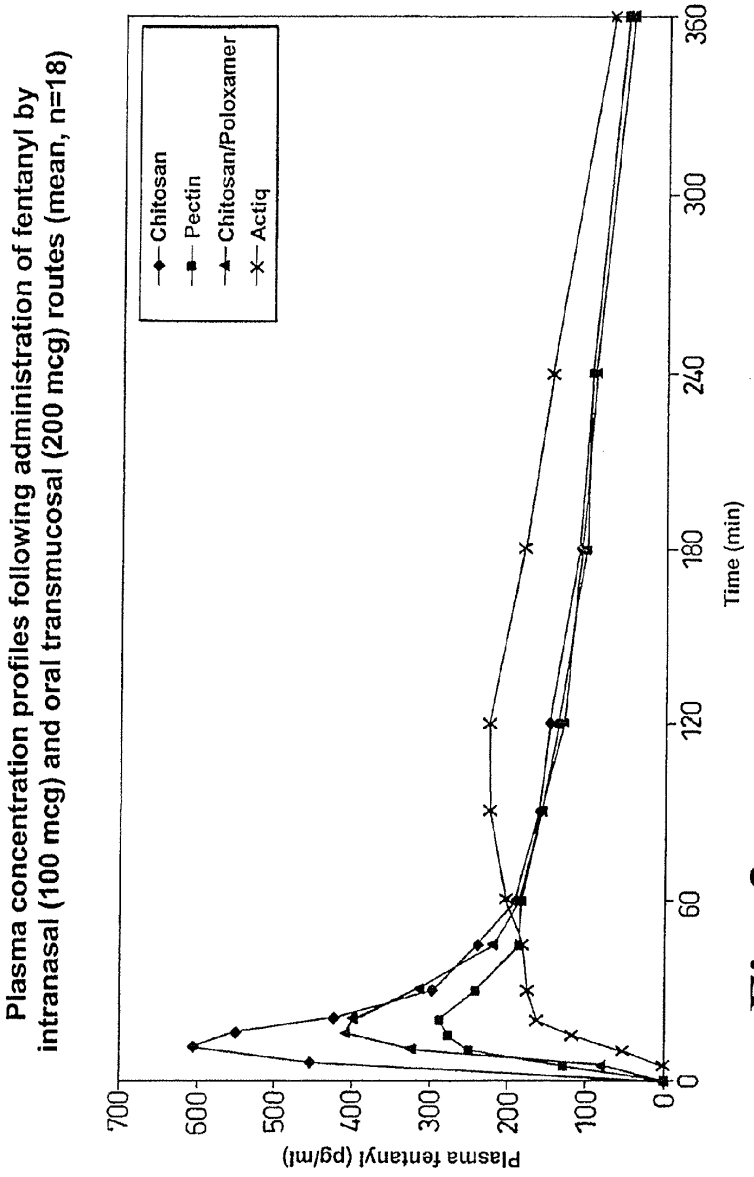

Fig. 2

INTRANASAL SPRAY DEVICE CONTAINING PHARMACEUTICAL COMPOSITION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 13/541,325, filed Jul. 3, 2012, now allowed, which is a division of U.S. patent application Ser. No. 12/047,388, filed Mar. 13, 2008, now U.S. Pat. No. 8,216,604, which in turn is a division of U.S. patent application Ser. No. 10/753,628, filed Jan. 8, 2004, now abandoned, the disclosures of each of which are hereby incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] This invention relates to pharmaceutical compositions for the intranasal administration of fentanyl.

[0003] The nasal route of drug delivery can afford rapid onset of action and convenience to patients and/or care giver. In particular, this route can provide rapid absorption of drugs into the blood circulation. In some cases absorption of almost the whole dose can be achieved and the pharmacokinetics can be similar to intravenous administration. Such rapid and effective drug delivery can be useful in the treatment of crisis situations such as pain, including breakthrough pain, headache and migraine (Nasal Systemic Drug Delivery, Chien et al. (eds), Dekker, New York, 1987).

[0004] Fentanyl (N-(1-phenethyl-4-piperidyl)propionanilide) is a potent opioid analgesic and may be used in the treatment of severe acute and chronic pain.

[0005] It has been reported that fentanyl is rapidly and well absorbed from the nasal cavity (Striebel et al., Brit. J. Anaesthesia, 96, suppl 1, 108, 1993). In addition, the effectiveness of intranasal fentanyl in providing analgesia in patients has been demonstrated in a number of studies (for example Striebel et al., Brit. J. Anaesthesia, 96, suppl 1, 108 and 109, 1993; Striebel et al., Anaesthesia, 48, 753-757, 1993; Majushree et al., Can. J. Anesth., 49, 190-193, 2002; Toussaint et al., Can. J. Anesth., 47, 299-302, 2000). In all of these studies the intranasal administration of fentanyl appears to have been achieved by dropping or spraying a commercially available injection formulation into the nose (SUBLIMAZE®, from Janssen). The commercially available injection formulation of fentanyl contains 0.05 mg of fentanyl, in the form of the citrate salt, in 1 ml of sodium chloride solution and necessitates the intranasal administration of a large volume of liquid in order to provide a therapeutically effective dose of drug.

[0006] Fentanyl is also currently available in a transdermal patch and a transmucosal lozenge. The transdermal patch (for example DUROGESIC® from Janssen) provides a steady concentration of fentanyl in plasma over a prolonged period and is not suitable for the rapid relief of severe pain, such as breakthrough pain associated with terminal illness or acute pain associated with trauma or following surgery. The transmucosal lozenge (ACTIQ®, Cephalon Inc) is used in the treatment of breakthrough pain and is available in a number of dose strengths ranging from 0.2 to 1.6 mg. The absorption of fentanyl from the transmucosal formulation is relatively slow. Times to achieve the peak plasma concentration (T_{max}) of from 20 to 480 minutes have been reported (pp. 405-409, Physician's Desk Reference, 54th edition, Medical Economics Company, Montvale, N.J., 2000).

[0007] Thus, there remains a need for alternative means for the delivery of fentanyl, for example via the intranasal route.

[0008] The listing or discussion of a prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

BRIEF SUMMARY OF THE INVENTION

[0009] The present invention provides a composition suitable for the intranasal administration of fentanyl that overcomes one or more of the problems described above, and a method of using it to treat or manage pain in a subject.

[0010] More specifically, the present invention relates to a method of treating or managing pain by intranasally administering to an animal in need thereof in an amount to effectively treat or manage pain a pharmaceutical composition comprising an aqueous solution of

[0011] fentanyl or a pharmaceutically acceptable salt thereof in an amount to effectively treat or manage pain and

[0012] a pectin having a degree of esterification (DE value) of less than 30%, provided that the composition is substantially free of divalent metal ions;

[0013] wherein the animal administered the composition is provided with a peak plasma concentration of fentanyl (C_{max}) that is from 10 to 80% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The foregoing summary, as well as the following detailed description of preferred embodiments of the invention, will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there is shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown.

[0015] In the drawings:

[0016] FIG. **1** shows mean plasma concentration profiles of fentanyl following the administration of a fentanyl solution comprising chitosan and a fentanyl solution that did not contain chitosan to sheep obtained in Example 7.

[0017] FIG. **2** shows plasma concentration of fentanyl profiles for three intranasal and one transmucosal formulation obtained in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

[0018] Surprisingly, it has been found that it is possible to administer fentanyl intranasally in a practical dose volume and provide rapid absorption in combination with a lower peak plasma concentration than that provided using a simple aqueous solution and an extended plasma concentration-time profile. These advantages can be achieved while maintaining a bioavailability that is comparable to that obtained by the intranasal administration of a simple aqueous solution comprising fentanyl.

[0019] By "comparable bioavailability," it is meant that the area under the plasma concentration vs. time curve (AUC) is at least 50%, more preferably at least 60% and most preferably at least 70% of that for a simple aqueous solution of fentanyl administered intranasally at the same dose.

[0020] By "simple aqueous solution," it is meant fentanyl and an ingredient to make the solution isotonic, such as man-

nitol, dextrose or sodium chloride, dissolved in water. A simple aqueous solution may optionally contain a preservative, such as benzalkonium chloride. An example of such a simple aqueous solution comprises 1.57 mg/ml fentanyl citrate, 48 mg/ml mannitol and 0.15 mg/ml benzalkonium chloride in water.

[0021] The present invention provides a composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof to an animal, which comprises an aqueous solution of

[0022] fentanyl or a pharmaceutically acceptable salt thereof and

[0023] a pharmaceutically acceptable additive selected from

[0024] a pectin and

[0025] a poloxamer and chitosan or a salt or derivative thereof;

[0026] provided that when the composition comprises a pectin it is substantially free of agents that cause the pectin to gel, such as divalent metal ions, especially calcium ions.

[0027] The additive may be a pectin, a poloxamer, a chitosan (or a salt or derivative thereof) or it may be a mix of two or more of these additives.

[0028] In comparison to a simple aqueous solution of fentanyl administered intranasally at the same dose, the compositions of the present invention provide a lowered peak plasma concentration of fentanyl (C_{max}) and optionally an extended plasma-concentration time profile. The peak plasma concentration (C_{max}) achieved using a composition of the present invention is from 10 to 80%, preferably from 20 to 75% and more preferably from 30 to 70% of that achieved using a simple aqueous solution administered intranasally at an identical fentanyl dose. This means, for example, if a simple aqueous solution of fentanyl produces a (C_{max}) of 1000 μg/ml, the (C_{max}) produced by a composition of this invention following administration of an identical dose of fentanyl, is in the range 100-800 μg/ml, preferably 200-750 μg/ml and more preferably 300-700 μg/ml.

[0029] The time to achieve the peak plasma concentration (T_{max}) by nasal administration of a composition of the present invention is preferably from 5 to 60 minutes, more preferably from 5 to 45 minutes and most preferably from 5 to 30 minutes.

[0030] Fentanyl is preferably used in the form of a pharmaceutically acceptable salt. Most preferably fentanyl citrate is used.

[0031] The concentration of fentanyl or a salt thereof in the compositions of the invention is preferably in the range of from 0.05 to 30 mg/ml, more preferably from 0.1 to 20 mg/ml and most preferably from 0.2 to 16 mg/ml (expressed as fentanyl base).

[0032] The term "pharmaceutically acceptable" is readily understood in the art and can be considered to include materials that may be used in commercially available pharmaceutical or food products and/or have GRAS (generally regarded as safe) status and/or are listed in a pharmacopoeia such as the United States Pharmacopoeia or the European Pharmacopoeia.

[0033] In one aspect, the present invention provides a composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, comprising an aqueous solution of fentanyl or a pharmaceutically acceptable salt thereof and a pectin and which provides a peak plasma concentration (C_{max}) of fentanyl of from 10 to 80% of that achieved using a simple aqueous solution administered intranasally at an identical fentanyl dose.

[0034] Pectins are polysaccharide substances present in the cell walls of all plant tissues. Commercially they are generally obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. Pectins are heterogeneous materials, comprising partially methoxylated polygalacturonic acids.

[0035] The proportion of galacturonic acid moieties in the methyl ester form represents the degree of esterification (DE). The term "DE" is well understood by those skilled in the art and may be represented as the percentage of the total number of carboxyl groups that are esterified, i.e., if four out of five acid groups is esterified this represents a degree of esterification of 80%, or as the methoxyl content of the pectin. The respective theoretical maximum for each is 100% and 16% respectively. "DE" as used herein refers to the total percentage of carboxyl groups that are esterified. The degree of esterification (DE) of pectins found naturally can vary considerably (from 60 to 90%).

[0036] Pectins can be categorized into those having a low degree of esterification (low methoxylation) or a high degree of esterification (high methoxylation). A "low DE" or "LM" pectin has a degree of esterification below 50% whereas a "high DE" or "HM" pectin has a degree of esterification of 50% or above.

[0037] The gelling properties of aqueous pectin solutions can be controlled by the concentration of pectin, the type of pectin, especially the degree of esterification of the galacturonic acid units, and the presence of added salts.

[0038] Preferably low DE pectins are used in the compositions of the present invention. More preferably pectins having a degree of esterification of less than 35%, for example from 5 to 35%, preferably from 7 to 30%, such as from about 10 to about 25%, for example from 15 to 25% are used in the present invention.

[0039] Low DE pectins are usually prepared by the de-esterification of extracted pectins, normally on a bench scale, by way of an enzymatic process, or, on an industrial scale, by treatment with acid or ammonia in an alcoholic heterogeneous medium. Treatment with ammonia creates so-called low DE amidated pectins. As used herein, the term "low DE pectin" includes both amidated and non-amidated low DE pectins.

[0040] Low DE pectins may be purchased commercially. An example of a low DE pectin which may be used in the present invention is SLENDID® 100, supplied by CP Kelco (Lille Skensved, Denmark) which has a degree of esterification of about 15 to 25%.

[0041] The primary mechanism by which low DE pectins gel in aqueous solution is through exposure to metal ions, such as those found in the nasal mucosal fluid as described in WO98/47535.

[0042] The solutions of the invention should not gel on storage. Thus, solutions containing a pectin are substantially free of agents that cause the pectin to gel, such as divalent metal ions, especially calcium ions. By "substantially free" of divalent metal ions it is meant greater than 97%, preferably greater than 99%, more preferably greater than 99.9% and especially greater than 99.99% free of divalent metal ions.

[0043] When a composition of the invention contains a pectin, the concentration of pectin is preferably in the range of from 1 to 40 mg/ml, more preferably from 2 to 30 mg/ml and most preferably from 5 to 25 mg/ml.

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