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(71) Applicant(s)

Archimedes Development Limited

(72) Inventor(s)

Watts, Peter James; Lafferty, William Columbus Ian; Castile, Jonathan David; Smith, Alan

(74) Agent/Attorney

Griffith Hack, Level 3 509 St Kilda Road, Melbourne, VIC, 3004

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(71) Applicant *(for all designated States except US)*: **WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTRE LIMITED** [GB/GB]; Albert Einstein Centre, Nottingham Science & Technology Park, University Boulevard, Nottingham NG7 2TN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CASTILE, Jonathan, David** [GB/GB]; West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited, Albert Einstein Centre, Nottingham Science & Technology Park, University Boulevard, Nottingham NG7 2TN (GB). **WATTS, Peter, James** [GB/GB]; West Pharmaceutical Services Drug Delivery & Clinical Research Centre Limited, Albert Einstein Centre, Nottingham Science & Technology Park, University Boulevard, Nottingham NG7 2TN (GB). **LAFFERTY, William, Columbus, Ian** [GB/GB]; 28 Nanpantan Road, Loughborough, Leicestershire LE11 3SU (GB). **SMITH, Alan** [GB/GB]; West Pharmaceutical Services Drug Delivery & Clini, cal Research Centre Limited, Albert Einstein Centre, Nottingham Science & Technology Park, University Boulevard, Nottingham NG7 2TN (GB).

(74) Agent: **CROWHURST, Charlotte**; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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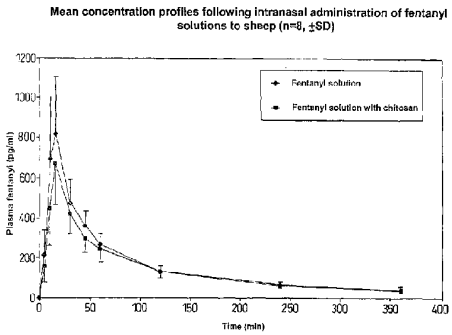
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING FENTANYL FOR INTRANASAL DELIVERY



(57) Abstract: This 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 (i) fentanyl or a pharmaceutically acceptable salt thereof and (ii) a pharmaceutically acceptable additive selected from (a) a pectin and (b) 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.

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PHARMACEUTICAL COMPOSITIONS

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

The nasal route of drug delivery can afford rapid onset of action and convenience to patients and/or carers. 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).

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.

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.

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, NJ, 2000).

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

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".

The present invention provides a composition suitable for the intranasal administration of fentanyl that overcomes one or more of the problems described above.

Surprisingly, we have 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. We have found that these advantages can be achieved while maintaining a bioavailibility that is comparable to that obtained by the intranasal administration of a simple aqueous solution comprising fentanyl.

By comparable bioavailability we mean 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.

By simple aqueous solution we mean fentanyl and an ingredient to make the solution isotonic, such as mannitol, 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 benzalknium chloride in water.

In one aspect, the present invention provides a composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, which comprises an aqueous solution of

(i) 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) and

(ii) from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less;

provided that the composition 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 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

In another aspect, the present invention provides a composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, which comprises an aqueous solution of

(i) 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl free base) and

(ii) 5 to 25 mg/ml of a pectin having a DE value of from 7 to 30%;

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and has a pH of from 3.4 to 5.0 and an osmolality of from 0.25 to 0.35 osmol/kg;

provided that the composition 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 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

In another aspect, the present invention provides use of a pharmaceutically acceptable additive which is from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less, in the manufacture of a medicament for the intranasal delivery of from 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) to a patient in need thereof, which medicament is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose provided that the composition is substantially free of divalent metal ions.

In another aspect, the present invention provides use of a pharmaceutically acceptable additive which is from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less, for intranasal delivery of from 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) to a patient in need thereof, which is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose provided that the composition is substantially free of divalent metal ions.

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 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 300-700 μg/ml.

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.

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

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.

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 hieterogeneous materials, comprising partially methoxylated polygalacturonic acids.

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 methoxy 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%).

Pectins can be categorised 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.

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.

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

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.

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%.

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 WO 98/47535.

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 we mean greater than 97%, preferably greater than 99%, more preferably greater than 99.9% and especially greater than 99.99% free of divalent metal ions.

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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.

A preferred pectin containing composition of the invention comprises 0.2 to 16 mg/ml of fentanyl (expressed as fentanyl base) and 5 to 25 mg/ml of a pectin having a DE value of from 7 to 30% and has a pH of from 3.4 to-5.0 and an osmolality of from 0.25 to 0.35 osmol/kg.

In one aspect, the present invention provides a composition comprising fentanyl or a pharmaceutically acceptable salt thereof and a poloxamer and chitosan or a salt or derivative thereof.

Poloxamers are block copolymers of ethylene oxide and propylene oxide. They have the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ wherein a is typically from 2 to 130 and b is typically from 15 to 67. Poloxamers have a number of pharmaceutical applications, such as viscosity modifiers, solubilising agents or emulsifiers. They may be used in the compositions of the present invention as thickening agents and in order to control and modify the absorption of fentanyl into the systemic circulation such that a peak plasma concentration (C_{max}) of fentanyl of from 30 to 70% of that achieved using a simple aqueous solution administered intranasally at an identical fentanyl dose is achieved.

Several different types of poloxamer are available commercially, from suppliers such as BASF, and vary with respect to molecular weight and the proportions of ethylene oxide "a" units and propylene oxide "b" units. Poloxamers suitable for use in the present invention typically have a molecular weight of from 2,500 to 18,000, for example from 7,000 to 15,000 Da. Examples of commercially available poloxamers suitable for use in the present invention include poloxamer 188, which structurally contains 80 "a" units and 27 "b" units, and has a molecular weight in the range 7680 to 9510 and poloxamer 407 which structurally contains 101 "a" units and 56 "b" units, and has a molecular weight in the range 9840 to 14600 (Handbook of Pharmaceutical Excipients, editor A. H. Kippe, third edition, Pharmaceutical Press, London, UK, 2000). Preferably the poloxamer is poloxamer 188.

When the compositions of the present invention comprise a poloxamer, the poloxamer is preferably present at a concentration in the range of from 50 to 200 mg/ml, more preferably from 65 to 160 mg/ml and most preferably from 80 to 120 mg/ml.

Compositions of the invention that comprise a poloxamer also comprise chitosan or a salt or derivative thereof.

Chitosans are cationic polymers that have mucoadhesive properties. The mucoadhesion is thought to result from an interaction between the positively charged chitosan molecule and the negatively charged sialic acid groups on mucin (Soane *et al*, Int. J. Pharm., 178, 55-65, 1999).

By the term "chitosan" we include all derivatives of chitin, or poly-N-acetyl-D-glucosamine, including all polyglucosamines and oligomers of

glucosamine materials of different molecular weights, in which the greater proportion of the N-acetyl groups have been removed through hydrolysis (deacetylation). Preferably, the chitosan is produced from chitin by deacetylation to a degree of greater than 40%, preferably between 50 and 98%, more preferably between 70% and 90%.

The chitosan, chitosan derivative or salt used in the present invention preferably has a molecular weight of 4,000 Da or more, preferably from 10,000 to 1,000,000 Da, more preferably from 15,000 to 750,000 Da and most preferably from 50,000 to 300,000 Da.

Salts of chitosan are suitable for use in the present invention. Suitable salts include, but are not limited to, the nitrate, phosphate, glutamate, lactate, citrate, hydrochloride and acetate salts. Preferred salts are chitosan glutamate and chitosan hydrochloride.

Chitosan derivatives are also suitable for use in the present invention. Suitable chitosan derivatives include, but are not limited to, ester, ether or other derivatives formed by bonding acyl and/or alkyl groups with the hydroxyl groups, but not the amino groups of chitosan. Examples are O-alkyl ethers of chitosan and O-acyl esters of chitosan. Modified chitosans, such as those conjugated to polyethylene glycol may be used in the present invention.

Low and medium viscosity chitosans suitable for use in the present invention may be obtained from various sources, including NovaMatrix, Drammen, Norway; Seigagaku America Inc., MD, USA; Meron (India) Pvt, Ltd., India; Vanson Ltd, VA, USA; and AMS Biotechnology Ltd., UK. Suitable derivatives include those that are disclosed in Roberts, Chitin Chemistry, MacMillan Press Ltd., London (1992).

Particularly preferred chitosan compounds that may be mentioned include the "Protosan™" types available from NovaMatrix, Drammen, Norway.

Preferably, the chitosan, or salt or derivative thereof is water-soluble.

An aqueous solution of chitosan may be prepared by dissolving chitosan base or a derivative of chitosan base in a pharmaceutically acceptable mineral or organic acid such as hydrochloric, lactic, citric or glutamic acid or by dissolving a chitosan salt or a salt of a chitosan derivative in water.

When the compositions of the present invention comprise chitosan, a chitosan salt or a chitosan derivative, the concentration of chitosan is preferably from 0.1 to 20 mg/ml, more preferably from 0.5 to 15 mg/ml and most preferably from 1 to 10 mg/ml (expressed as chitosan base).

A preferred poloxamer and chitosan containing composition of the invention comprises 0.2 to 16 mg/ml of fentanyl (expressed as fentanyl base), 80 to 120 mg/ml of a poloxamer having a molecular weight of from 7,000 to 15,000 Da and 1 to 10 mg/ml (expressed as chitosan base) of a chitosan having a molecular weight of from 50,000 to 300,000 Da or a salt or derivative thereof and has a pH of from 3.0 to 5.0 and an osmolality of from 0.4 to 0.7 osmol/kg.

The pH of the compositions of the invention may be regulated. For example, buffered aqueous solutions may be used. Alternatively, the pH of the compositions of the present invention may be adjusted using any pharmaceutically acceptable acidifying or alkalising agent that is compatible with the other components of the compositions. Examples of suitable pharmaceutically acceptable acidifying agents include, but are not

limited to, hydrochloric acid, acetic acid, citric acid, methane sulphonic acid, lactic acid, tartaric acid, fumaric acid and malic acid. Examples of pharmaceutically acceptable alkalising agents include, but are not limited to, sodium hydroxide, potassium hydroxide, meglumine, tromethamine, sodium bicarbonate, monoethanolamine, diethanolamine and triethanolamine. When the composition of the invention contains pectin, in order to prevent unwanted gelling, the acidifying agent or alkalising agent preferably should not contain an alkali metal or alkaline earth metal ion, for example it should not be sodium hydroxide, potassium hydroxide or sodium bicarbonate.

The pH of the compositions of the invention is generally preferably from 3 to 6. For the pectin containing compositions of the invention, the pH is more preferably from 3.2 to 5.5 and most preferably from 3.4 to 5.0. For the poloxamer and chitosan containing compositions of the invention, the pH is more preferably from 3.0 to 5.5 and most preferably from 3.0 to 5.0.

To ensure that the compositions of the invention are well tolerated by the patient when administered to the nose (for example when sprayed into the nasal cavity), it is advantageous that they have an osmolality close to that of plasma. The osmolality is generally preferably from 0.1 to 1.0 osmol/kg. For the pectin containing compositions of the invention, the osmolality is more preferably from 0.2 to 0.8 osmol/kg, still more preferably from 0.2 to 0.4 osmol/kg and most preferably from 0.25 to 0.35 osmol/kg. For the poloxamer and chitosan containing compositions of the invention, the osmolality is more preferably from 0.2 to 0.9 osmol/kg, still more preferably from 0.3 to 0.8 osmol/kg and most preferably from 0.4 to 0.7 osmol/kg.

The osmolality of the compositions of the invention may be adjusted to the desired value by adding any appropriate agent. Salts of metal ions, in particular sodium chloride, are commonly used to adjust the osmolality of pharmaceutical preparations. However, it is not appropriate to use metal ions when the composition of the invention includes a pectin because pectins may form a gel in the presence of metal ions. We have also found that addition of metal ions, for example sodium in the form of sodium chloride, to compositions containing fentanyl and chitosan results in the formation of a precipitate. Thus, the use of metal ion containing agents should preferably be avoided. We have found that gel formation in pectin-containing fentanyl compositions and precipitate formation in chitosan-containing fentanyl compositions can be avoided by using a non-metal ion containing compound such as a polyhydric alcohol, for example mannitol or sorbitol, or a sugar, for example dextrose, sucrose or trehalose, to adjust the osmolality. Especially preferred agents to adjust osmolality are mannitol and dextrose at a concentration of up to 50 mg/ml.

The compositions of the invention may also contain other ingredients such as antioxidants (for example sodium metabisulphite), chelating agents (such as edetic acid or one of its salts), preservatives (such as benzalkonium chloride, sorbic acid or one of its salts, phenylethyl alcohol and/or propyl hydroxybenzoate), sweeteners (such as saccharin or aspartame), flavourings (such as peppermint) or other agents generally used in pharmaceutical liquid preparations and well known to those skilled in the art.

Preferably, the compositions of the invention contain a preservative or are sterile.

Preferably, the compositions of the invention are non-pyrogenic.

The composition of the invention can be administered to the nasal cavity in any suitable form, for example in the form of drops or sprays.

Methods suitable for administering a composition to the nasal cavity will be well known by the person of ordinary skill in the art. Any suitable method may be used. The preferred method of administration is the use of a spray device. Spray devices can be single (unit) dose or multiple dose systems, for example comprising a bottle, pump and actuator, and are available from various commercial sources including Pfeiffer, Valois, Bespak and Becton-Dickinson. Electrostatic spray devices, such as described in US 5,655,517, are also suitable for the intranasal administration of the compositions of the present invention.

For a spray device, the typical volume of liquid that is dispensed in a single spray actuation is in the range of from 0.01 to 0.15 ml. A typical dosing regimen for a nasal spray product would be in the range of one spray into a single nostril to two sprays into each nostril.

The preferred dose of fentanyl or one of its salts is from 0.01 to 5.0 mg (10 to 5000 μg), more preferably from 0.015 to 4.0 mg (15 to 4000 μg) and most preferably from 0.02 to 3.0 mg (20 to 3000 μg).

The present invention also provides a spray device loaded with a composition as defined above.

The present invention also provides a process for preparing a composition as described above. This process comprises mixing the components of the composition in water. Purified water such as water for injections may be used.

The compositions of this invention can be used for the treatment, management or prevention of both acute and chronic pain, in animals including humans. The compositions of the invention can be used to treat, manage or prevent pain a wide variety of pain conditions such as those associated with injury and accident trauma, terminal illness, especially breakthrough pain, and following surgery.

The present invention also provides the use of a pharmaceutically acceptable additive selected from

(a) a pectin and

(b) a poloxamer and chitosan or a salt or derivative thereof;

in the manufacture of a medicament for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof to an animal such as a human in need thereof, which medicament is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

In particular, the present invention provides the use of a pharmaceutically acceptable additive selected from

(a) a pectin and

(b) a poloxamer and chitosan or salt or derivative thereof;

in the manufacture of a medicament for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof to an animal such as a human in need thereof suitable for the treatment, prevention or management of acute or chronic pain, which medicament is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

In the figures:

Figure 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.

Figure 2 shows plasma concentration of fentanyl profiles for three intranasal and one transmucosal formulation obtained in Example 8.

The invention is illustrated by the following non-limiting examples.

EXAMPLES

Example 1 - Solution containing 1.57 mg/ml fentanyl citrate (equivalent to 1 mg/ml fentanyl base) and 10 mg/ml pectin

2 g of pectin (Slendid 100, CP Kelco, Denmark) was dissolved with stirring in 180 ml of water. 1 ml of phenylethyl alcohol (R. C. Treat, UK) and 40 mg of propyl hydroxybenzoate (Nipa Laboratories, UK) were added to the pectin solution as preservatives. 314 mg of fentanyl citrate (MacFarlan Smith, Edinburgh, UK) and 8.3 g of mannitol (Sigma, Poole, UK) were dissolved in the pectin solution, the solution transferred to a 200 ml volumetric flask and made up to volume with water. The pH of the solution was 4.2 and the osmolality was 0.33 osmol/kg.

Example 2 – Solution containing 1.57 mg/ml fentanyl citrate and 20 mg/ml pectin

4 g of pectin (Slendid 100) was dissolved with stirring in 180 ml of water. 1 ml of phenylethyl alcohol and 40 mg of propyl hydroxybenzoate were added to the pectin solution. 314 mg of fentanyl citrate and 8.3 g of mannitol were dissolved in the pectin solution, the solution was transferred to a 200 ml volumetric flask and made up to volume with water.

4 ml of the solution was transferred into a 5 ml glass bottle. A Valois VP7 spray pump (0.1 ml volume) with actuator (Valois, France) was attached to bottle. The pump was primed by firing several times. When primed, firing the device delivered 0.1 ml of liquid spray containing 0.157 mg of fentanyl citrate (equivalent to 0.1 mg of fentanyl base).

Example 3 – Solution containing 1.57 mg/ml fentanyl citrate, 100 mg/ml poloxamer 188 and 5 mg/ml chitosan glutamate

A 15 mg/ml benzalkonium chloride solution was prepared by weighing 300 mg of 50% benzalkonium chloride aqueous solution (Albright & Wilson, UK) into a 10 ml volumetric flask, dispersing it in approximately 8 ml of water, then making the solution up to 10 ml with water.

2.5 ml of 15 mg/ml benzalkonium chloride solution and 200 ml of water were added to 25 g of poloxamer 188 in a beaker. The beaker was placed in an ice bath and the contents stirred until the poloxamer had dissolved. 1.25 g of chitosan glutamate (Protasan UPG213, Pronova, Norway) and 11.25 g of mannitol were stirred into the poloxamer solution until dissolved. 393 mg of fentanyl citrate was dissolved in approximately 10 ml of water and

added to the poloxamer solution. The solution was transferred into a 250 ml volumetric flask and made up to volume with water.

The pH of the solution was 3.3 and the osmolality was 0.56 osmol/kg.

0.123 ml samples of the final solution were filled into the glass vial of a single dose nasal spray device (Unitdose System, Pfeiffer, Germany). The vial was sealed with a rubber closure and assembled into the device. On firing, the device emitted 0.1 ml of liquid spray containing a 0.157 mg dose of fentanyl citrate (equivalent to 0.1 mg fentanyl base).

Example 4 – Solution containing 6.28 mg/ml fentanyl citrate (equivalent to 4 mg/ml fentanyl base) and 10 mg/ml pectin

2.5 g of pectin (Slendid 100) was dissolved with stirring in 200 ml of water. 1.25 ml of phenylethyl alcohol and 50 mg of propyl hydroxybenzoate were added to the pectin solution. 1.58 mg of fentanyl citrate and 9 g of mannitol were dissolved in the pectin solution, the solution transferred to a 250 ml volumetric flask and made up to volume with water.

The pH of the solution was 3.8 and the osmolality was 0.30 osmol/kg.

0.123 ml samples of the final solution were filled into the glass vial of a single dose nasal spray device (Unitdose System, Pfeiffer, Germany). The vial was sealed with a rubber closure and assembled into the device. On firing, the device emitted 0.1 ml of liquid spray containing a 0.628 mg dose of fentanyl citrate (equivalent to 0.4 mg fentanyl base).

Example 5 – Preparation of solution containing 1.57 mg/ml fentanyl citrate

78.5 mg of fentanyl citrate was dissolved in 40 ml of water. 0.5 ml of 15 mg/ml benzalkonium chloride solution and 2.4 g mannitol were added to the fentanyl solution which was stirred until all of the ingredients had dissolved. The solution was transferred to a 50 ml volumetric flask and made up to volume with water.

Example 6 – Preparation of solution containing 1.57 mg/ml fentanyl citrate and 5 mg/ml chitosan glutamate

250 mg of chitosan glutamate was dissolved in 40 ml of water. 0.5 ml of 15 mg/ml benzalkonium chloride solution, 78.5 mg fentanyl citrate and 2.4 g mannitol were added to the chitosan solution which was stirred until all of the ingredients had dissolved. The solution was transferred to a 50 ml volumetric flask and made up to volume with water.

Example 7 – Pharmacokinetic performance of fentanyl intranasal formulations in the sheep

The solutions prepared in Examples 5 and 6 were administered intranasally to sheep. A group of 8 animals, each weighing approximately 60 kg, was used. The doses were administered to a randomised crossover design and each animal received 0.3 ml of each test solution (equivalent to 0.3 mg fentanyl base) intranasally. Nasal doses were administered via a spray device with the dose volume being divided equally between both nostrils.

Blood samples were collected and plasma separated. Plasma samples were assayed by a LC-MS-MS method for fentanyl content.

Mean plasma concentration-time curves for the two nasal test solutions are shown in Figure 1. The curves were essentially identical and indicated that fentanyl was rapidly absorbed both in the absence and presence of chitosan.

Example 8 - Pharmacokinetic performance of fentanyl intranasal and oral transmucosal formulations in human volunteers

A clinical study was performed to evaluate the pharmacokinetic performance of three intranasal fentanyl formulations and a transmucosal lozenge formulation (Actiq®, Elan Pharmaceuticals, UK).

The intranasal formulations were prepared as described Examples 1, 3, and 6 above.

The study was a randomised four-way complete cross-over trial in a group of 18 healthy adult volunteers. Intranasal doses were administered using Pfeiffer Unitdose devices. Each subject received a single spray into one nostril to provide a fentanyl dose of 0.1 mg. The Actiq® dose was provided as a lozenge containing 200 µg (0.2 mg) of fentanyl. The lozenge was administered by dissolving in the mouth over a period of approximately 15 minutes. Plasma samples were collected from the subjects and analysed for fentanyl content using a LC-MS-MS assay. Pharmacokinetic parameters were calculated from the plasma data.

Plasma concentration versus time curves for the three intranasal and one transmucosal formulation are shown in Figure 2. A summary of the pharmacokinetic parameters is provided in Table 1.

Table 1. Summary of mean fentanyl pharmacokinetic parameters.

Formulation	T_{max} (min)	C_{max} (pg/ml)	AUC (pg/ml.h)	Bioavailibility relative to Actiq® (%)
Nasal chitosan solution	12	647	95747	166
Nasal pectin solution	21	337	87079	147
Nasal poloxamer + chitosan solution	18	442	82614	143
Actiq® (oral transmucosal)	101	264	117840	(100)

Based on the results from the sheep study described in Example 7, the pharmacokinetic performance of the chitosan solution in the human volunteer study can be considered to be representative of a simple aqueous solution of fentanyl. The intranasal formulations containing pectin and a mixture of poloxamer and chitosan were able to reduce the C_{max} to values of 52% and 68% respectively relative to the nasal chitosan solution.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, which comprises an aqueous solution of

(i) from 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) and

(ii) from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less;

provided that the composition 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 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

2. A composition according to claim 1, comprising a pharmaceutically acceptable salt of fentanyl.

3. A composition according to claim 2, wherein the pharmaceutically acceptable salt of fentanyl is fentanyl citrate.

4. A composition according to any one of the preceding claims, wherein the pectin has a DE value of from 5 to 30%, from 7 to 30%, or from about 10 to about 25%.

5. A composition according to any one of the preceding claims, wherein the concentration of the pectin is from 2 to 30 mg/ml, or from 5 to 25 mg/ml.

6. A composition according to any one of the preceding claims wherein the total % of the composition is at least 99% free of divalent metal ions.

7. A composition according to any one of the preceding claims having an osmolality of from 0.25 to 0.35 osmol/kg.

8. A composition according to any one of the preceding claims having a pH of from 3.4 to 5.0.

9. A composition for the intranasal delivery of fentanyl or a pharmaceutically acceptable salt thereof, which comprises an aqueous solution of

(i) 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl free base) and

(ii) 5 to 25 mg/ml of a pectin having a DE value of from 7 to 30%; and has a pH of from 3.4 to 5.0 and an osmolality of from 0.25 to 0.35 osmol/kg;

provided that the composition 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 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose.

10. A composition according to any one of the preceding claims which is adapted to be delivered to the nose in the form of drops or as a spray.

11. A composition according to any one of the preceding claims for use in the treatment or prevention of acute or chronic pain.

12. The use of a pharmaceutically acceptable additive which is from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less, in the manufacture of a medicament for the intranasal delivery of from 0.2 to 16 mg/ml fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) to a patient in need thereof, which medicament is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose provided that the composition is substantially free of divalent metal ions.

13. Use according to claim 12 wherein the pectin has a DE value of from 7 to 30%, or from about 10 to about 25%.

14. Use of a composition according to any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of acute or chronic pain.

15. A method for the treatment or prevention of acute or chronic pain, which method comprises the intranasal delivery of a composition according to any one of claims 1 to 11 to a patient.

16. A spray device loaded with a composition according to any one of claims 1 to 11.

17. A process for preparing a composition according to any one of claims 1 to 11, which process comprises mixing fentanyl or a pharmaceutically acceptable salt thereof with the pectin having a degree of esterification (DE value) of 30% or less in water.

18. The use of a pharmaceutically acceptable additive which is from 1 to 40 mg/ml of a pectin having a degree of esterification (DE value) of 30% or less, for intranasal delivery of from 0.2 to 16 mg/ml of fentanyl or a pharmaceutically acceptable salt thereof (expressed as fentanyl base) to a patient in need thereof, which is adapted to provide a peak plasma concentration of fentanyl (C_{max}) that is from 30 to 70% of that achieved using a simple aqueous solution of fentanyl administered intranasally at an identical fentanyl dose provided that the composition is substantially free of divalent metal ions.

19. Use according to claim 18, wherein the pectin has a DE value of from 5 to 25%, or from 7 to 30%.

20. Use according to claims 12 or 13 or claims 18 or 19 for the treatment or prevention of acute or chronic pain.

21. A composition according to any one of claims 1 to 11, use according to any one of claims 12 to 14 or 18 to 20, a method according to claim 15, a spray device

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according to claim 16, or a process according to claim 17, substantially as herein described with reference to any of the Examples and/or Figures.

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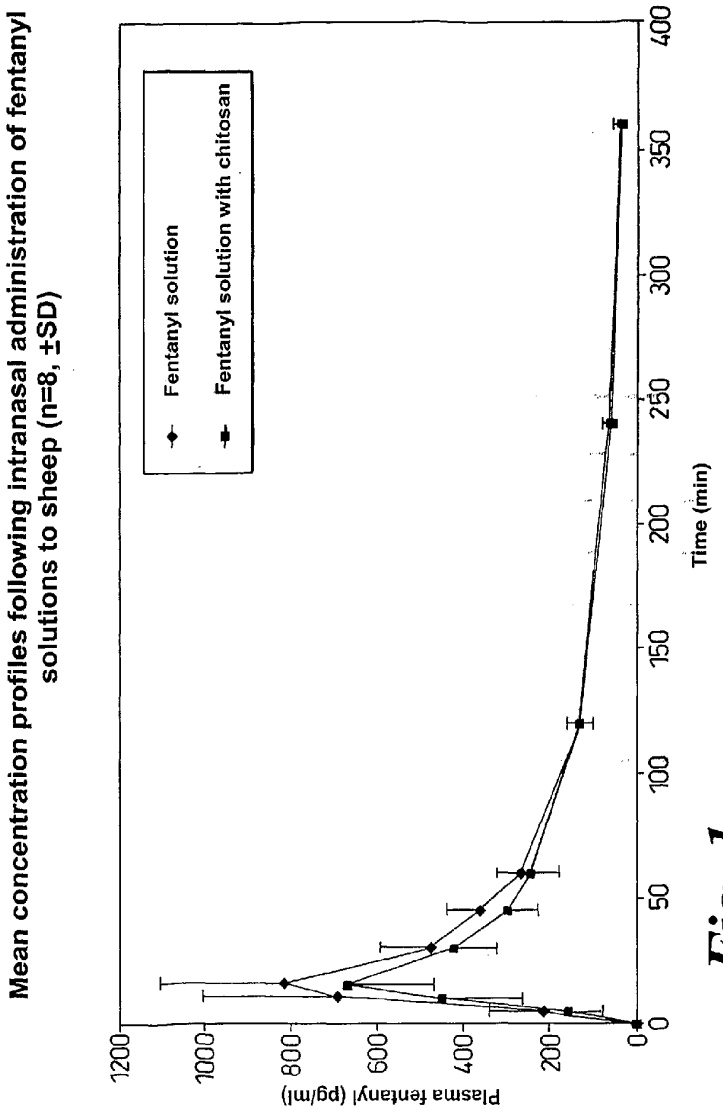
Mean concentration profiles following intranasal administration of fentanyl solutions to sheep (n=8, ±SD)
Fentanyl solution
Fentanyl solution with chitosan
Plasma fentanyl (pg/ml)
Time (min)
0
200
400
600
800
1000
1200
0
50
100
150
200
250
300
350
400

Fig. 1

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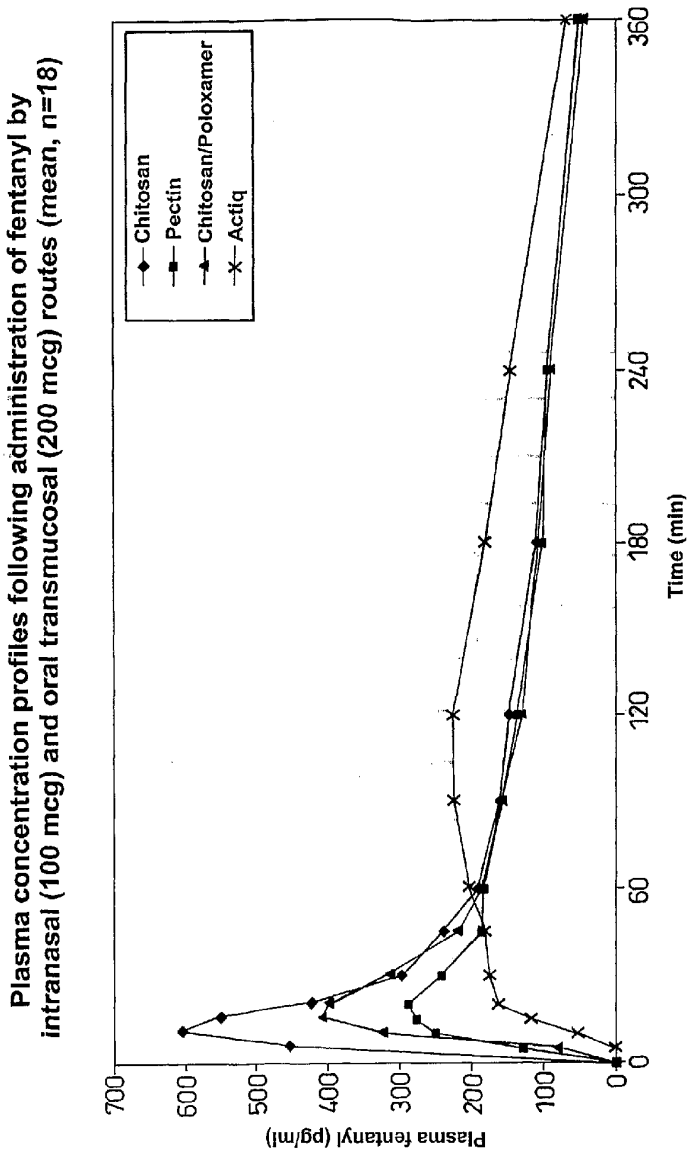
Plasma concentration profiles following administration of fentanyl by intranasal (100 mcg) and oral transmucosal (200 mcg) routes (mean, n=18)
Chitosan
Pectin
Chitosan/Poloxamer
Actiq
Plasma fentanyl (pg/ml)
0
100
200
300
400
500
600
700
Time (min)
0
60
120
180
240
300
360

Fig. 2