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(54) **Title:** NON-AQUEOUS OIL-BASED FENTANYL COMPOSITIONS FOR TRANSMUCOSAL ADMINISTRATION

(57) **Abstract:** The invention provides a composition and method of treating pain using the composition, the composition comprising a solution of at least one active agent selected from the group consisting of fentanyl, a derivative of fentanyl and an analogue of fentanyl in at least one non-aqueous oil-based solvent for transmucosal administration.

NON-AQUEOUS OIL-BASED FENTANYL COMPOSITIONS FOR TRANSMUCOSAL ADMINISTRATION

TECHNICAL FIELD

The invention described herein relates generally to anesthesia and analgesia. In particular, the invention is directed to transmucosal administration of a non-aqueous composition containing fentanyl or its derivatives, including nasal administration, although the scope of the invention is not necessarily limited thereto.

BACKGROUND ART

Fentanyls are extensively used for anesthesia and analgesia, most often in the operating room and intensive care unit. Fentanyl transdermal patch is used in chronic pain management. Fentanyl patches work by releasing fentanyl into body fats, which then slowly release the drug into the blood stream over 72 hours, allowing for long lasting relief from pain.

Fentanyl lozenges are a solid formulation of fentanyl citrate on a stick in the form of a lollipop that dissolves slowly in the mouth for transmucosal absorption. These lozenges are intended for opioid-tolerant individuals and are effective in treating breakthrough cancer pain.

Small fentanyl buccal pellets have also been developed. These are effervescent tablets placed in the cheek and is absorbed through the buccal mucosa. One advantage of such tablets is claimed to be quicker absorption into the bloodstream at lower dosage levels.

Fentanyl is frequently given intrathecally as part of spinal anesthesia or epidurally for epidural anesthesia and analgesia. It is also used as a sedative.

It has been shown that fentanyl administered transmucosally or intranasally is effective in the relief of postoperative pain and cancer pain. Transmucosal and intranasal delivery of low concentrations and low doses of fentanyl have been performed.

Animal data shows rapid occurring absorption by use of the transmucosal and particularly the nasal route. Transmucosal and nasal routes would therefore be suitable for use in patients requiring rapid relief from severe pain. General advantages of transmucosal and nasal application aiming at systemic effect are ease of self-administration, supporting a health-

economic argument and the self-care concept. In addition, first pass liver metabolism and gastro-intestinal metabolism are avoided.

WO2002/009707 describes intranasal delivery of fentanyl in aqueous solutions. Although effective, fentanyl and derivatives are not particularly soluble in water. In addition, absorption of the active agent from an aqueous solution is not optimal.

Therefore, there would be an advantage if it were possible to provide a composition for transmucosal administration of fentanyl and its derivatives, which may overcome at least some of the above-mentioned disadvantages or provide a useful or commercial choice.

SUMMARY OF THE INVENTION

The invention provides compositions of fentanyl and derivatives in non-aqueous formulation with unexpected advantages over the compositions disclosed in the prior art.

In a first embodiment, the invention provides a composition for transmucosal administration, the composition comprising a solution of at least one active agent selected from the group consisting of fentanyl, a derivative of fentanyl and an analogue of fentanyl in at least one non-aqueous oil-based solvent.

In a second embodiment, the invention provides a method of treating pain in a subject, the method comprising transmucosal administration of a composition comprising at least one active agent selected from the group consisting of fentanyl, a derivative of fentanyl and an analogue of fentanyl, in a non-aqueous oil-based solvent.

With regard to the first and second embodiments as defined above, the composition comprises fentanyl or a derivative thereof, such as alfentanyl, sulfentanyl, remifentanyl, carfentanyl and ohmefentanyl, or the salts of fentanyl and the derivatives. Optionally, the composition comprises a mixture of fentanyl and one or more fentanyl derivative.

The concentration of active agent in the composition can be any practicable concentration but is preferably from 1μg/ml to 100mg/ml.

The solvent of the invention can be any practicable non-aqueous oil-based solvent, such as vegetable oils, for example olive oil, almond oil, peppermint oil, macadamia oil, eucalyptus oil, canola oil, cottonseed oil, peanut oil and soybean oil; or other equivalents of a

pharmacopoeial nature, for example paraffin liquid, glycerine, polyethylene glycol, polypropylene glycol. The solvent of the invention is preferably glycerine (glycerol), paraffin liquid, olive oil or almond oil.

The composition can further comprise a fragrance component, such as an ester, scented oil, or artificial scent. The addition of a fragrance ensures that a user of the composition knows when it has been administered. In addition, the composition can then not be administered without subject knowledge, and patient compliance is improved due to a pleasant smell on application of the composition.

The composition can also further comprise a preservative such as benzyl alcohol, LiquaPar® Oil (ISP Corporation), benzalkonium chloride, EDTA, benzethonium chloride, chlorobutanol, parabens and phenoxyethanol, to allow for inclusion of the composition in a device for multi-dose administration. Preferably, the preservative is LiquaPar® Oil, parabens, benzyl alcohol or benzalkonium chloride.

Transmucosal administration can be effected by any practicable manner, but is preferable effected by nasal administration.

The nasal administration of the composition can be effected in any practicable manner, including by swab, droplets, or spray. The composition is preferably administered by spray, from a suitable spray device. The device can be of any appropriate configuration, and is preferably a device which delivers a spray volume of between 1 µl and 1 ml per actuation of the device. An example of such a device is a Valois® VP7 pump, or the Valois Freepod™ system.

The invention therefore provides a composition of fentanyl or derivatives thereof with enhanced solubility, drug delivery and drug uptake, which necessitates lower doses of the active and consequent lower incidence of side effects. The non-aqueous oil-based solvent also increases the stability of the active in solution, ensuring a longer shelf-life and preservation of activity of the composition.

The optional inclusion of a fragrance acts as an identifier for both healthcare workers and patients to increase safety of administration and patient compliance.

In order that the invention may be more readily understood and put into practice, one or more preferred embodiments thereof will now be described, by way of example only.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Examples

Formulations of the invention are made in the following manner:

1. Preserved Formulations:

Fentanyl	2.5	mg
LiquaPar Oil	0.02	mL
Olive Oil	q.s.5.0	mL
Fentanyl	5.0	mg
LiquaPar Oil	0.02	mL
Olive Oil	q.s.5.0	mL
Fentanyl	2.5	mg
LiquaPar Oil	0.02	mL
Vanillin BP	25.0	mg
Almond Oil	q.s.5.0	mL
Fentanyl	5.0	mg
LiquaPar Oil	0.02	mL
Vanillin BP	25.0	mg
Almond Oil	q.s.5.0	mL

2. Unpreserved Formulations:

Fentanyl	2.5	mg
Vanillin BP	25.0	mg
Glycerol	q.s.5.0	mL
Fentanyl	5.0	mg
Vanillin BP	25.0	mg
Glycerol	q.s.5.0	mL

3. Pediatric Formulations:

Fentanyl	1.0	mg
Vanillin BP	25.0	mg

Glycerol	q.s.5.0	mL
Fentanyl	1.0	mg
LiquaPar Oil	0.02	mL
Vanillin BP	25.0	mg
Almond Oil	q.s.5.0	mL

The composition is packaged in a glass vial of Type 1 clear or amber glass of volume from 0.1 milliliter up to 100 milliliters of the type typically used for an injection pharmaceutical.

The composition may also be packaged in a single use device of the type manufactured by Valois or equivalent such as the Valois Monodose™ or Dolphin™. Typically the volume of a single-use container is between 0.1 and 2 milliliters

Efficacy and Uses of Formulations

Fentanyl is highly lipid soluble and stable in such a non-aqueous liquid phase. It has an octanol-water partition coefficient (drug lipid-solubility study method) several thousand times higher than morphine, a readily water soluble opiate drug.

Fentanyl's high solubility in non-aqueous solutions can improve the uptake of the drug via the transmucosal and particularly the nasal route.

Using a non-aqueous system allows the formulator to use the exact quantity of fentanyl base for formulation, thereby reducing errors and reducing salts of addition for some water-soluble versions of fentanyl, for example fentanyl citrate.

A non-aqueous formulation is retained for a prolonged period on the mucosa, particularly the nasal mucosa, when compared to an aqueous formulation.

A non-aqueous formulation can mask the unpleasant taste experienced at the back of the throat upon application of an opioid-containing nasal spray.

A non-aqueous formulation ensures the drug cannot be easily misused by mixing with other solutions, for example a non-aqueous solution of fentanyl would not be miscible with an alcoholic drink and therefore a potential 'date-rape' victim would be alerted to the presence of that formulation in such a drink.

Non-aqueous based transmucosal and nasal sprays have more comfortable feel on administration, avoiding the "cold" feeling of an aqueous system.

Non-aqueous formulations can assist with inclusion of a fragrance to improve drug safety and compliance.

It is clear from the foregoing that the invention provides an improved composition of fentanyl and/or its derivatives for transmucosal administration. The invention provides a composition of fentanyl or derivatives thereof with enhanced solubility, drug delivery and drug uptake, which necessitates lower doses of the active and consequent lower incidence of side effects. Stability of the active in solution is also increased. In addition, optional inclusion of a fragrance acts as an identifier for both healthcare workers and patients to increase safety of administration and patient compliance. Also, optimal inclusion of a preservative allows for provision of a multi-dose formulation.

The foregoing embodiments are illustrative only of the principles of the invention, and various modifications and changes will readily occur to those skilled in the art. The invention is capable of being practiced and carried out in various ways and in other embodiments. It is also to be understood that the terminology employed herein is for the purpose of description and should not be regarded as limiting.

The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

The claims defining the invention are as follows:

1. A composition for transmucosal administration, the composition comprising a solution of at least one active agent selected from the group consisting of fentanyl, a derivative of fentanyl and an analogue of fentanyl,l in at least one non-aqueous oil-based solvent.

2. The composition of claim 1 wherein the at least one active agent is selected from the group consisting of fentanyl, alfentanyl, sulfentanyl, remifentanyl, ohmefantanyl and carfentanyl in at least one non-aqueous oil-based solvent.

3. The composition of claim 1 or claim 2 wherein the concentration of the active agent is from 1μg/ml to 100mg/ml.

4. The composition of any one of claims 1 to 3 wherein the at least one solvent is a plant oil.

5. The composition of claim 4 wherein the at least one solvent is selected from the group consisting of olive oil, almond oil, peppermint oil, macadamia oil, eucalyptus oil, canola oil, cottonseed oil, peanut oil, coconut oil, castor oil(s), grapeseed oil, soybean oil, other vegetable and nut oils.

6. The composition of any one of claims 1 to 3 wherein the at least one solvent is selected from the group consisting of a glycol, paraffin liquid and glycerine.

7. The composition of any one of claims 1 to 6 further comprising a fragrance.

8. The composition of claim 7 further comprising a preservative.

9. The composition of any one of claims 1 to 8 wherein the administration is intranasal.

10. A method of treating pain in a subject, the method comprising transmucosal administration of a composition comprising at least one active agent selected from the group consisting of fentanyl, a derivative of fentanyl and an analogue of fentanyl, in a non-aqueous oil-based solvent.

11. The method of claim 10 wherein the at least one active agent is selected from the group consisting of fentanyl, alfentanyl, sulfentanyl, remifentanyl, carfentanyl and ohmefentanyl in a non-aqueous oil-based solvent.

12. The method of claim 10 or claim 11 wherein the concentration of the active agent is from 1μg/ml to 100mg/ml.

13. The method of any one of claims 10 to 12 wherein the solvent is a plant oil.

14. The method of claim 13 wherein the at least one solvent is selected from the group consisting of olive oil, almond oil, peppermint oil, macadamia oil, eucalyptus oil, canola oil, cottonseed oil, peanut oil, coconut oil, castor oils, grapeseed oil,soybean oil, other vegetable oils, and other nut oils.

15. The method of any one of claims 10 to 12 wherein the at least one solvent is selected from the group consisting of a glycol, paraffin liquid and glycerine.

16. The method of any one of claims 10 to 15 further comprising a fragrance.

17. The method of claim 16 further comprising a preservative.

18. The method of any one of claims 10 to 17 wherein the administration is intranasal.

19. The method of claim 18 wherein administration is via a spray device.

20. The method of claim 19 wherein the spray device delivers a unit-dose of the active agent upon actuation of between 0.001mL to 2mL.

21. The method of claim 19 wherein the spray device delivers a multi-dose of the active agent upon actuation of between 0.001mL to 2mL.

AMENDED CLAIMS
received by the International Bureau on 12 March 2009 (12.03.2009)

1. A composition for transmucosal administration, the composition comprising a solution of at least one active agent selected from the group consisting of fentanyl and a derivative of fentanyl in a single non-aqueous oil-based solvent, wherein the composition excludes water.

2. The composition of claim 1 wherein the at least one active agent is selected from the group consisting of fentanyl, alfentanyl, sulfentanyl, remifentanyl, ohmefantanyl and carfentanyl.

3. The composition of claim 1 or claim 2 wherein the concentration of the active agent is from 1μg/ml to 100mg/ml.

4. The composition of any one of claims 1 to 3 wherein the single solvent is a plant oil.

5. The composition of claim 4 wherein the single solvent is selected from the group consisting of olive oil, almond oil, peppermint oil, macadamia oil, eucalyptus oil, canola oil, cottonseed oil, peanut oil, coconut oil, castor oil(s), grapeseed oil, soybean oil, other vegetable and nut oils.

6. The composition of any one of claims 1 to 3 wherein the single solvent is selected from the group consisting of a glycol, paraffin liquid and glycerine.

7. The composition of any one of claims 1 to 6 further comprising a fragrance.

8. The composition of claim 7 further comprising a preservative.

9. The composition of any one of claims 1 to 8 wherein the administration is intranasal.

10. A method of treating pain in a subject, the method comprising transmucosal administration of a composition comprising at least one active agent selected from the group consisting of fentanyl and a derivative of fentanyl in a single non-aqueous oil-based solvent, wherein the composition excludes water.

11. The method of claim 10 wherein the at least one active agent is selected from the group consisting of fentanyl, alfentanyl, sulfentanyl, remifentanyl, carfentanyl and ohmefentanyl.

12. The method of claim 10 or claim 11 wherein the concentration of the active agent is from 1μg/ml to 100mg/ml.

13. The method of any one of claims 10 to 12 wherein the solvent is a plant oil.

14. The method of claim 13 wherein the solvent is selected from the group consisting of olive oil, almond oil, peppermint oil, macadamia oil, eucalyptus oil, canola oil, cottonseed oil, peanut oil, coconut oil, castor oils, grapeseed oil, soybean oil, other vegetable oils, and other nut oils.

15. The method of any one of claims 10 to 12 wherein the solvent is selected from the group consisting of a glycol, paraffin liquid and glycerine.

16. The method of any one of claims 10 to 15 further comprising a fragrance.

17. The method of claim 16 further comprising a preservative.

18. The method of any one of claims 10 to 17 wherein the administration is intranasal.

19. The method of claim 18 wherein administration is via a spray device.

20. The method of claim 19 wherein the spray device delivers a unit-dose of the active agent upon actuation of between 0.001mL to 2mL.

21. The method of claim 19 wherein the spray device delivers a multi-dose of the active agent upon actuation of between 0.001mL to 2mL.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2008/001779

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 31/4468 (2006.01) *A61P 29/02* (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIDS, Medline, CAplus and keywords: fentanyl, oil, glycol, paraffin, intranasal, transmucosal and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/009707 A1 (NYCOMED DANMARK A/S) 7 February 2002 See the abstract, page 7 lines 9-15, 17-21, page 8 line 34 to page 9 line 11, page 13 line 20 to page 14 line 30, examples 2 and 3 on pages 28-31	1-21
X	WO 2005/117830 A1 (CAMURUS AB) 15 December 2005 See the abstract, page 5 line 31 to page 6 line 31, page 10 line 31 to page 15 line 10, page 26 lines 13-16, example 37 on page 48	1-21
X	US 2004/0115133 A1 (WERMELING) 17 June 2004 See the abstract, paragraphs 26, 28, 29, 30, 36, 42-44, 136 and table at end of right column page 10	1-21
X	US 2007/0225379 A1 (CARRARA et al.) 27 September 2007 See the abstract, paragraphs 31, 33, 37, 70 and example formulations 8-11 on page 9 right column	1-3, 6-12, 15-21

☐ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2009	3 FEB 2009
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **LEAH WALKER** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6225 6170

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2008/001779

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2002009707	AU	81746/01	CA	2417727	CN	1466455
		CN	101181241	EE	200300050	EP	1307194
		EP	1642578	IS	6702	JP	2008044951
		KR	20080053423	NO	20030365	NZ	524396
		PL	365053	US	2004034059	US	2007134164
WO	2005117830	AU	2005249274	AU	2005324794	BR	PI0511807
		CA	2569513	CA	2594710	CA	2594711
		CA	2594718	CA	2609810	CN	101014319
		CN	101217940	EP	1768650	EP	1843746
		EP	1845942	EP	1848403	EP	1888031
		KR	20070046815	KR	20070104599	US	2007265190
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		CA	2536582	CA	2560024	CN	1972691
		EP	1370212	EP	1663112	EP	1727549
		US	6610271	US	2001055571	US	2003077300
		US	2003206867	US	2004176359	US	2006083691
		US	2006147386	US	2007071687	US	2007209660
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US	2007225379	AR	030312	AU	82064/01	AU	2004220498
		AU	2004283431	BR	PI0408153	BR	PI0414551
		CA	2418135	CA	2515426	CA	2538856
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US	2007166361	WO	0211768	WO	2004080413
WO	2005039531	WO	2008012071	ZA	200505985

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX