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(54) **NOVEL COMPOSITIONS**

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(57) **ABSTRACT**

Compositions and method are provided, for the treatment of pain, e.g. acute breakthrough pain, by means of a systemic, non-invasive mode of administration. Specifically, the invention relates to a sublingual presentation of an opioid analgesic, such as fentanyl, or its salts, in amounts that are sufficient to treat the pain.

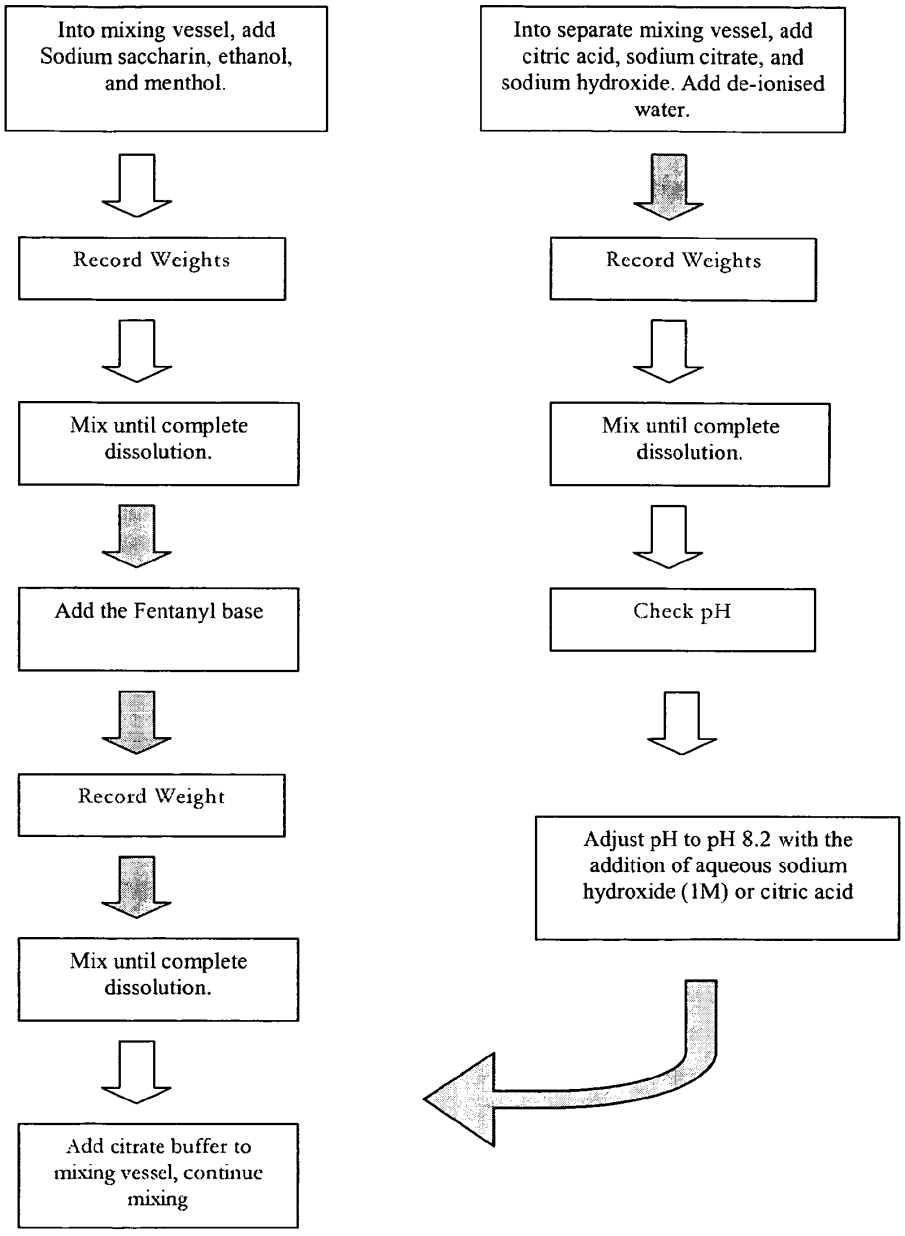

Fig. 1

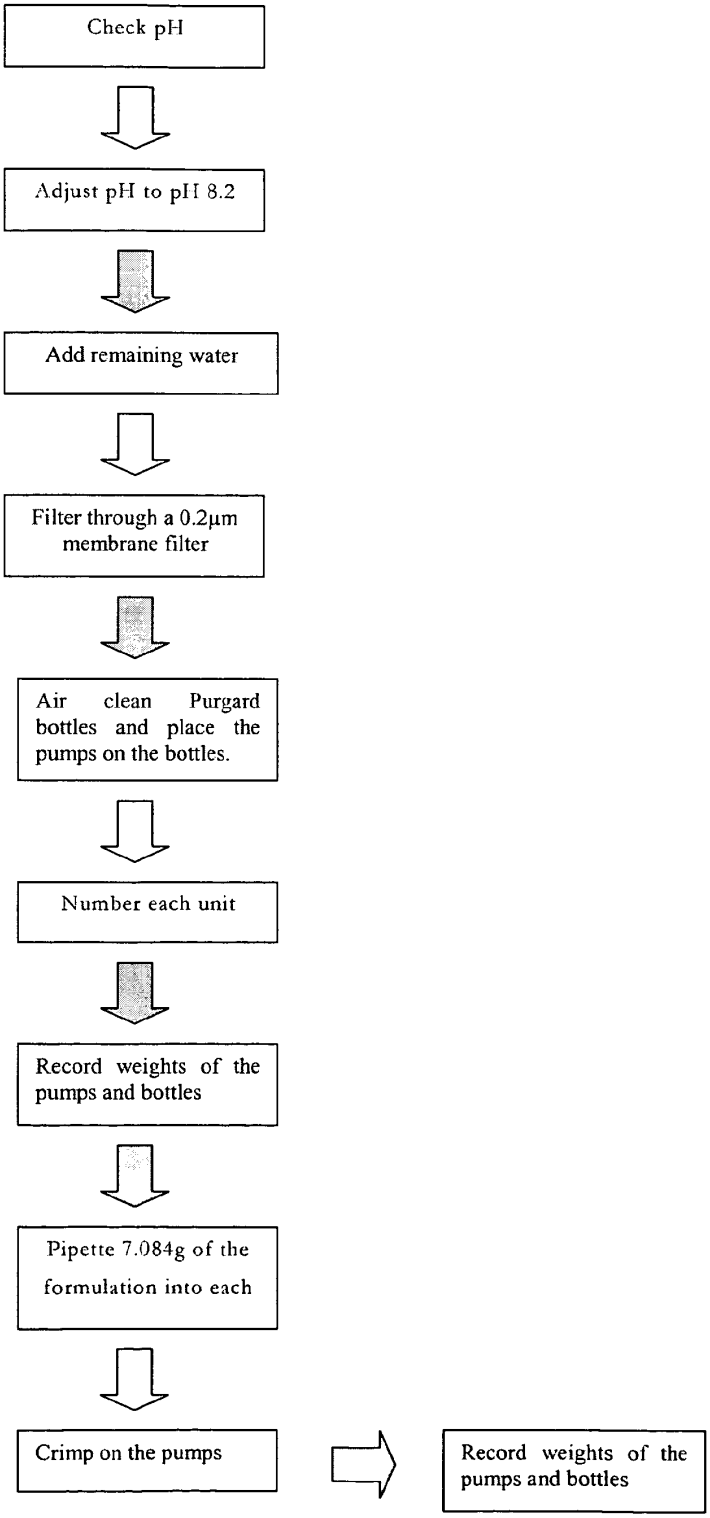

Fig. 2

NOVEL COMPOSITIONS

CROSS-REFERENCE TO EARLIER APPLICATION

[0001] This application is a continuation-in-part application of International Application PCT/GB04/01037, filed Mar. 11, 2004; which claims priority to GB 0305579.5, filed Mar. 11, 2003 and GB 0328023.7, filed Dec. 3, 2003. The subject application further claims priority to GB 0420173.7, filed Sep. 10, 2004, all of which are hereby incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

[0002] This invention relates to formulations of opioid analgesics and in particular fentanyl, especially pump spray formulations suitable for sublingual delivery.

BACKGROUND OF THE INVENTION

[0003] Opioid analgesics are useful in the treatment of pain, such as breakthrough pain. When treating pain, it is particularly attractive for the patient to be able to self-medicate, enabling specific pain episodes to be treated, as opposed to ongoing treatment when there may be no pain to treat. It is highly desirable for the onset of analgesia to occur as soon after administration of the opioid analgesic as possible, especially where the patient is self-medicating. This not only provides pain relief as soon as possible but it can also reduce the risk of overdosage. A delay in the onset of the therapeutic effect may prompt the patient to take a further dose, with the consequent risk of the serious side-effects associated with overdosage.

[0004] In the case of breakthrough pain, the onset of pain is relatively quick, usually between just a few seconds and 10 to 15 minutes, the median being approximately 3 minutes. The duration of breakthrough pain episodes tends to be anywhere between 5 minutes and 2 hours, the median being between 20 and 60 minutes.

[0005] Thus, for the most effective treatment of pain, and in particular, breakthrough pain, the analgesic effect should have a rapid onset. What is more, the analgesic effect should last for the duration of the pain episode. That said, administration of a second or further dose may be acceptable, provided that these additional doses have a rapid onset of effect, so that the pain is not left untreated for too long.

[0006] Fentanyl is a narcotic alkaloid, which has been used for many years as an anaesthetic and an analgesic, especially in the treatment of moderate to severe pain. Whilst undoubtedly effective for pain relief, and especially in the treatment of pain which is refractive to other treatments, there are a number of issues of clinical management associated with the use of fentanyl in therapy.

[0007] Foremost amongst these issues is the potential for serious side-effects with fentanyl. It has a much higher potency than commonly known narcotics and therefore it is necessary to ensure that it is being used within the established therapeutically effective range and to monitor patients for evidence of self-medication at greater than the recommended amount. Overdosage with fentanyl can lead to a number of undesirable and indeed life-threatening side-effects, predominantly hypoventilation and respiratory depression.

[0008] A number of routes of administration of a medicament can be associated with rapid onset of action. For example, WO90/07333 describes aerosol formulations of fentanyl, which are adapted for inhalation. However, these formulations suffer disadvantages such as their use of hydrofluorocarbon propellants and delivery effected by metered dose inhalers. In the case of the former, the disadvantages include high velocity which results in "bounce-back" on administration to the front of the mouth, cold sensations on administration and the risk of inhalation; for the latter, careful co-ordination of breath and actuation by the patient. When metered dose inhalers are used, a significant proportion of the delivered dose tends to impact the back of the throat from where it is swallowed rather than finding its way into the bronchial passages. Accordingly, the pharmacology of the medication may be unpredictable due to poor bioavailability following oral administration or may be characterised by a bi-phasic profile (fast initial onset as a result of the inhaled dose and a slower, late effect due to oral absorption of fentanyl). Furthermore, manufacture of the bulk formulation involves the preparation of large quantities of pressurised volatile propellant containing a potent narcotic analgesic. Accordingly, the precautions required to ensure safe manufacture are onerous and expensive.

[0009] WO95/31182 describes solution formulations of fentanyl in aerosol propellants intended for administration to patients by the pulmonary route.

[0010] WO01/97780 describes solution formulations of fentanyl free base in propellants, typically HFA134a, for sublingual aerosol administration.

[0011] WO00/47203 describes formulations of fentanyl citrate for intra-oral administration employing oral absorption enhancers.

[0012] Certain aqueous formulations of fentanyl for intranasal administration employing water and phosphate buffer have been described; see Paech, M. J., Lim, C. B., Banks, S. L., Rucklidge, M. W. M. & Doherty, D. A. (2003) Anaesthesia 58 (8), 740-744, and Lim et al (2003) J Pharm Practice Research 33, 59-63. Such formulations can suffer problems of nasal irritation associated with medium to long term usage via this route which is undesirable. Weinberg et al (1988) Clin Pharmacol Therap 44 335-342, discloses formulations of fentanyl employing water and phosphate buffer for sublingual administration, but these formulations are not advocated for use as a spray.

[0013] It is well known that the application of carefully chosen medicaments to the sublingual mucosa offers a route of administration which is capable of resulting in very rapid transmission of medicament to the bloodstream with consequent fast onset of effect. A number of ways of administering compositions sublingually are known. For example, tablets or liquids may be held under the tongue prior to swallowing. Another method is spray delivery. Of these various types of sublingual administration, spray delivery is preferred as it does not involve holding the composition under the tongue for an extended period of time as, for example, with a lozenge, and it reduces the amount of material which is swallowed (and may enter the blood stream in a delayed manner via the gastrointestinal tract). Pharmaceutical compositions, for example a fentanyl lozenge, cause increased salivation, which facilitates the unwanted swallowing of drug substance.

[0014] In the past, spray devices, including pump sprays, have been proposed for sublingual administration. However, their effect has not been properly optimised. In order to reduce the amount of the dispensed composition which fails to contact the sublingual mucosa, the compositions tend to be dispensed in a focussed manner, so that the sublingual spray devices have a tendency to administer the compositions to a relatively small part of the sublingual mucosa. This means that the composition is effectively concentrated in the relatively small area, which slows down absorption and also means that some of the composition may not be absorbed, but rather may be washed away by saliva and swallowed. This is a particular problem in the case of lipophilic opioid analgesics such as fentanyl. It has been shown that the lipophilic drugs need to be finely spread over the sublingual mucosa in order for them to be properly absorbed. When they are concentrated at a small area of the sublingual mucosa, absorption is reduced.

[0015] It is an aim of the present invention to provide a formulation, which avoids or mitigates some or all of the above-mentioned disadvantages.

[0016] Another aim of the present invention is to provide a presentation of an opioid analgesic for treating pain, and in particular breakthrough pain, wherein the opioid analgesic is administered via the sublingual route and the presentation preferably exhibits improved performance compared to known opioid analgesic compositions, including those which may be administered sublingually and intravenously. In particular, it is an aim of the invention to provide fast onset of therapeutic effect, together with an advantageous pharmacokinetic response and drug plasma profile which will avoid the disadvantages associated with the fast onset observed when opioid analgesics are administered intravenously.

SUMMARY OF THE INVENTION

[0017] The present invention is based at least in part on the understanding that spray delivery, having low volume and ability to target the sublingual mucosa, largely mitigates problems associated with other formulations, and can avoid the use of propellants.

[0018] According to the invention, a pharmaceutical composition, preferably a partially pressurised liquid spray formulation, comprises:

[0019] (a) fentanyl or a pharmaceutically acceptable salt thereof;

[0020] (b) water as carrier; and

[0021] (c) a polar organic solvent in sufficient amount to enhance the solubility of the fentanyl or pharmaceutically acceptable salt thereof in the water.

[0022] The formulations of the invention may be used in analgesia and for the treatment of pain. They are preferably administered sublingually as a spray. The formulations are well tolerated when administered to the sensitive sublingual mucosa and the sublingual spray administration will result in rapid onset of the therapeutic effect of the fentanyl.

[0023] The present invention also provides a pharmaceutical composition for use in the treatment of acute breakthrough pain by means of a systemic, non-invasive mode of administration. Specifically, the invention relates to a sublingual presentation of an opioid analgesic, such as fentanyl, or its salts, in amounts that are sufficient to treat the acute pain. Advantageously, the presentation of the opioid analgesic provides a rapid onset of action, as well as a pharmacokinetic response and drug plasma profile suitable to achieve optimal pain relief over the duration of symptoms with minimized side-effects.

[0024] The invention also relates to a specific drug formulation, dispensed using a metered pump action spray which is specifically designed for delivery via the sublingual route. This affords significant improvements and advantages in terms of plasma bioavailability and pharmacokinetic profile compared to similar, but non-optimised, propellant-driven aerosol formulations. These benefits relate in particular to:

[0025] i) a faster rate of onset of effect;

[0026] ii) a faster rate of offset of effect; and

[0027] iii) a faster Tmax.

[0028] According to a further aspect of the invention, an opioid analgesic pharmaceutical composition provides an opioid analgesic plasma concentration of 250 pg/ml within a period of no more than 2 hours, following sublingual administration using a pump spray dispensing device. The opioid analgesic is preferably fentanyl.

[0029] Amongst the advantages of these formulations is the fact that, by being water-based, they avoid the issues associated with using pressurised hydrofluorocarbon propellants as mentioned above. The formulations may be partially pressurised and are free of propellants such as volatile chlorofluorocarbons (e.g. propellant 12), volatile hydrofluoroalkanes (e.g. 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane) and volatile alkanes (e.g. propane or butane) and other substances which have significant vapour pressure at ambient temperature and pressure.

[0030] Furthermore the formulations of the present invention are characterised by good long-term physical and chemical stability.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] **FIG. 1** is a flow-chart showing the first stage of a method of preparing a formulation comprising 400 μg fentanyl.

[0032] **FIG. 2** is a flow-chart showing the second stage of the method.

DESCRIPTION OF THE INVENTION

[0033] The present invention provides a sublingual presentation of an opioid analgesic, such as fentanyl, which enables pain relief to be achieved very rapidly following administration of the drug.

[0034] In one embodiment of the present invention, the formulation is a solution, rather than a suspension. Whilst it is possible to spray a suspension, the fact that most suspensions settle means that the amount of active agent included in the dispensed dose will be variable and this can be highly undesirable. Although the effect of the settling of the suspension can be reduced to an extent by shaking the compo-

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