Exhibit 1005

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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.

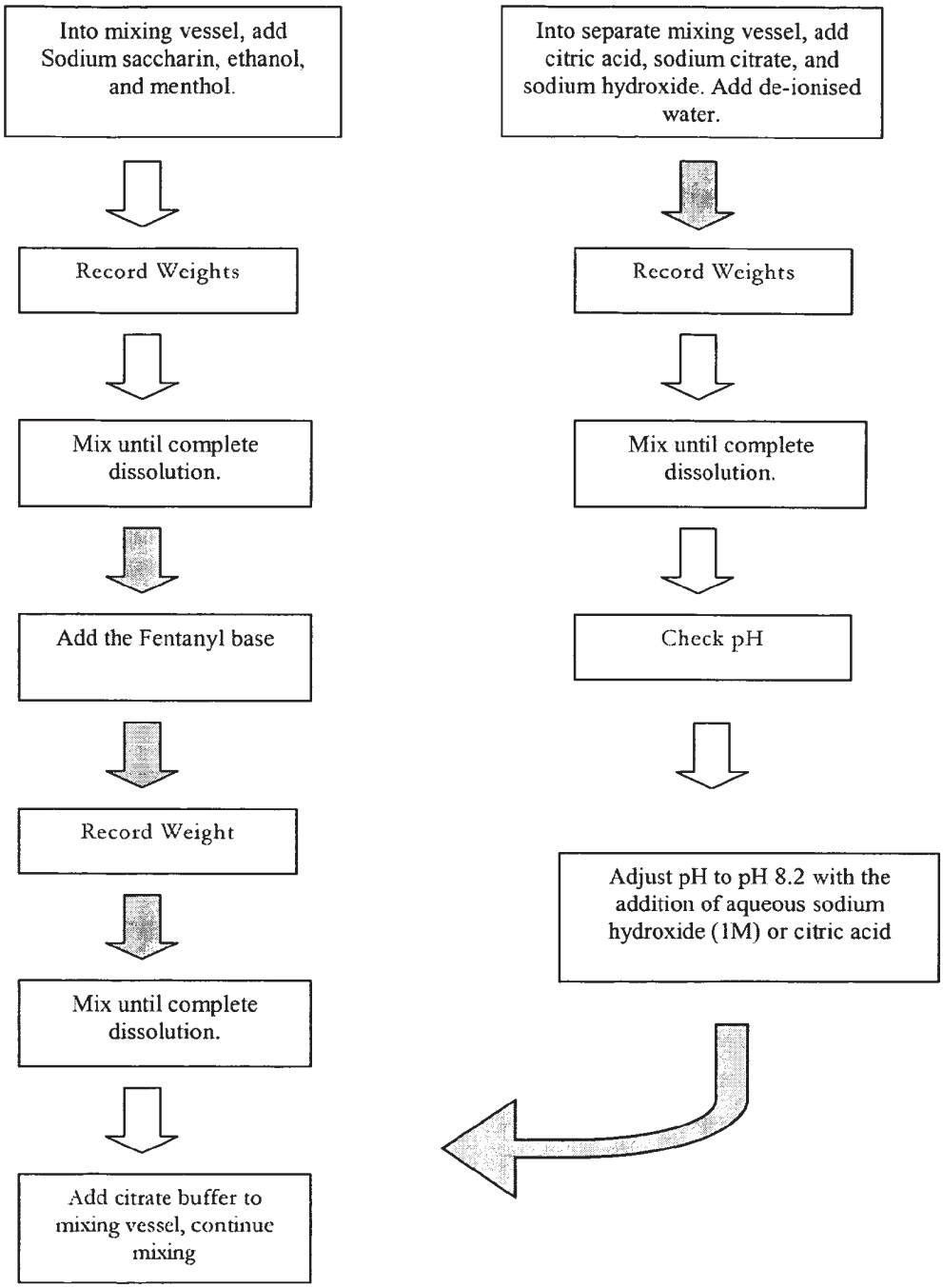

Fig. 1

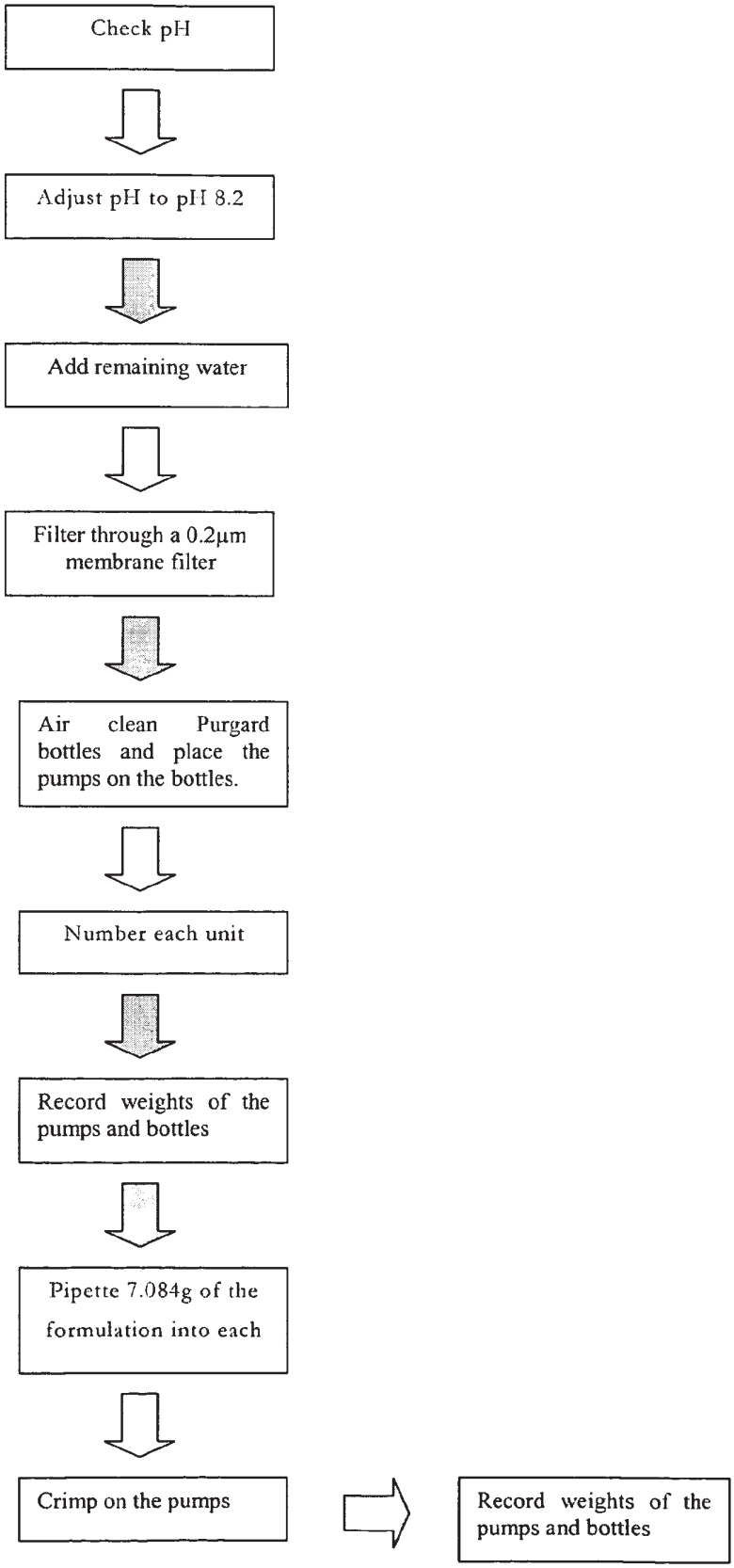

Fig. 2

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.

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