Claims

1. A pharmaceutical composition suitable for sublingual delivery, as well as rapid release of alfentanil therefrom and/or rapid uptake of alfentanil through the oral mucosa, which comprises a mixture comprising:

(a) microparticles of alfentanil, or a pharmaceutically acceptable salt thereof, which microparticles are presented on the surfaces of larger carrier particles;

(b) a ~~water-soluble~~ weak base; and

(c) a compound which is a weak acid, which acid is presented in intimate mixture with the microparticles of alfentanil or salt thereof, by being presented either:

(1) within the carrier particles, such that said carrier particles comprise a composite of:

(i) said acid material; and

(ii) another carrier particle material; or

(2) upon the surfaces of the carrier particles.

2. A composition as claimed in Claim 1, wherein the acid is citric acid.

3. A composition as claimed in any one of the preceding claims, wherein the ~~water-soluble~~ weak base comprises a phosphate, such as trisodium phosphate.

4. A composition as claimed in any one of the preceding claims, wherein the carrier particles comprise mannitol.

5. A pharmaceutical composition as claimed in any one of the preceding claims, which further comprises a disintegrant.

6. A composition as claimed in Claim 5, wherein the disintegrant is a superdisintegrant selected from croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone or a mixture thereof.

7. A composition as claimed in any one of the preceding claims wherein the base is water-soluble.

~~7~~8. A composition as claimed in any one of the preceding claims which is in the form of a tablet suitable for sublingual administration.

~~8~~9. A process for the preparation of a composition as defined in any one of Claims 1 to ~~7~~8, which comprises dry mixing carrier particles with alfentanil or salt thereof.

~~9~~10. A process for the preparation of a ~~sublingual tablet~~composition as defined in Claim ~~7~~8, which comprises directly compressing or compacting a composition as defined in any one of Claims 1 to 6.

~~10. A method of treatment of pain, which method comprises administration of a composition as defined in any one of Claims 1 to 7 to a person suffering from, or susceptible to pain.~~

11. A composition as defined in any one of Claims 1 to ~~7~~8 for use in the ~~a method of~~ treatment of pain.

12. The use of a composition as defined in any one of Claims 1 to ~~7~~8 for the manufacture of a medicament for ~~a method of~~the treatment of pain.

13 A ~~method as claimed in Claim 10, a~~ composition as claimed in Claim 11, or a use as claimed in Claim 12, wherein the pain is moderate to severe pain.

14. A ~~method,~~ composition or use as claimed in Claim 13, wherein the treatment is short term.

15. A ~~method,~~ composition or use as claimed in Claim 13 or Claim 14, wherein the pain is associated with a diagnostic, a surgical or a care-related procedure.

16. A ~~method,~~ composition or use as claimed in Claim 15 wherein the composition is administered not more than about 20 minutes prior to the procedure.

17. ~~A method of treatment of pain~~A composition or use as defined in any one of Claims ~~10 or 13~~11 to 16, ~~which~~wherein the ~~method of~~ treatment of pain comprises sublingual administration to a human patient in need of treatment of a pharmaceutical composition comprising between about 30 µg and about 3,000 µg of alfentanil or a pharmaceutically acceptable salt thereof, wherein said administration gives rise to a plasma concentration-time curve after said administration that posseses:

(I) a t_{max} (time to maximum plasma concentration) that is between about 10 and about 25 minutes after said administration; and/or

(II) a t_{last} (time to last measurable plasma concentration) that is not more than about 300 minutes after said administration; and, optionally,

(III) a C_{max} (maximum plasma concentration) that is between about 10 and about 100 ng per mL of plasma.

18. A ~~method~~composition or use as claimed in Claim 17 which comprises administration of a composition as defined in any one of Claims 1 to ~~7~~8.

Effervescent opioid containing formulations are disclosed in *inter alia* US patent applications 2005/0142197, 2005/0142198, 2007/0036853 and 2011/0071181,

International patent application WO 99/24023 discloses a sublingual tablet comprising an opioid, such morphine, mannitol and citric acid (in addition to sodium citrate).

There are currently no commercially-available solid state oral dosage formulations comprising the opioid analgesic alfentanil. It is instead administered intravenously as a sterile, non-pyrogenic, preservative free aqueous solution in a concentration of 500 µg alfentanil base per mL. The solution contains (as the only excipient) sodium chloride for isotonicity. To the applicant's knowledge, no short- or long-term stability issues have been reported for alfentanil solutions for injection.

We have surprisingly found that, when attempting to formulate alfentanil into a solid state, tablet formulation, a notable instability results. This instability is unexpectedly solved by the addition of a small amount of weak acid, such as citric acid, provided that that acid is presented in intimate mixture with the API.

Further, we have also found that a weak base, such as a sodium phosphate, may also be added to such formulations to enhance absorption and, even more surprisingly, that:

(a) the presence of the weak base does not, as expected, have a detrimental effect on the stability of the alfentanil in such formulations; and

(b) the enhanced absorption provided by the presence of the weak base is not, as expected, abrogated or cancelled out by the presence of the weak acid in such formulations.

According to ~~a first aspect of~~ the ~~invention~~present disclosure, there is provided a pharmaceutical composition suitable for sublingual delivery which comprises a mixture comprising:

(a) microparticles of alfentanil, or a pharmaceutically acceptable salt thereof, which microparticles are presented on the surfaces of larger carrier particles;

(b) a water-soluble weak base, such as a phosphate; and

(c) a compound which is a weak acid, which acid is presented in intimate mixture with the microparticles of alfentanil or salt thereof.

Such compositions are referred to hereinafter as "the compositions of the ~~invention~~disclosure".

In a first aspect, there is provided a pharmaceutical composition suitable for sublingual delivery, as well as rapid release of alfentanil therefrom and/or rapid uptake of alfentanil through the oral mucosa, which comprises a mixture comprising:

(a) microparticles of alfentanil, or a pharmaceutically acceptable salt thereof, which microparticles are presented on the surfaces of larger carrier particles;

(b) a weak base; and

(c) a compound which is a weak acid, which acid is presented in intimate mixture with the microparticles of alfentanil or salt thereof, by being presented either:

(1) within the carrier particles, such that said carrier particles comprise a composite of:

(i) said acid material; and

(ii) another carrier particle material; or

(2) upon the surfaces of the carrier particles.

In another aspect, there is provided a process for the preparation of a composition as defined above, which comprises dry mixing carrier particles with alfentanil or salt thereof.

In another aspect, there is provided a composition as defined above for use in the treatment of pain.

In another aspect, there is provided the use of a composition as defined above for the manufacture of a medicament for the treatment of pain.

In another aspect, there is provided a composition or use as defined above, wherein the treatment of pain comprises sublingual administration to a human patient in need of treatment of a pharmaceutical composition comprising between

about 30 µg and about 3,000 µg of alfentanil or a pharmaceutically acceptable salt thereof, wherein said administration gives rise to a plasma concentration-time curve after said administration that posseses:

(I) a t_{max} (time to maximum plasma concentration) that is between about 10 and about 25 minutes after said administration; and/or

(II) a t_{last} (time to last measurable plasma concentration) that is not more than about 300 minutes after said administration; and, optionally,

(III) a C_{max} (maximum plasma concentration) that is between about 10 and about 100 ng per mL of plasma.

Alfentanil and pharmaceutically-acceptable salts thereof are presented in the compositions of the invention in the form of microparticles. Microparticles preferably possess a weight based mean diameter, number based mean diameter and/or a volume based mean diameter of between about 0.5 µm and about 30 µm, e.g. about 15 µm, such as between about 1 µm and about 10 µm. As used herein, the term "weight based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by weight, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the weight fraction, as obtained by e.g. sieving (e.g. wet sieving). As used herein, the term "number based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by number, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the number fraction, as measured by e.g. microscopy. As used herein, the term "volume based mean diameter" will be understood by the skilled person to include that the average particle size is characterised and defined from a particle size distribution by volume, i.e. a distribution where the existing fraction (relative amount) in each size class is defined as the volume fraction, as measured by e.g. laser diffraction.

Microparticles of active ingredient may be prepared by standard micronisation techniques, such as grinding, jet milling, dry milling, wet milling, precipitation, etc. An air elutriation process may be utilised subsequently to prepare specific size fractions, if required.

Preferred salts of alfentanil include hydrochloride salts.

Weakly acidic materials that may be mentioned include those that, when dissolved in water and/or saliva, enable the provision (at the site of