buprenorphine, it might be possible to reduce the amount of this active pharmaceutical ingredient, giving rise to less opioid in the formulation and so reducing the amount available for injection if diverted by way of intravenous abuse.

International patent applications WO 00/16751, WO 2004/067004, WO 2006/103418 and WO 2008/068471 all disclose drug delivery systems for the treatment of e.g. acute pain by sublingual administration, applying an interactive mixture principle, in which the active ingredient in microparticulate form is adhered to the surfaces of larger carrier particles in the presence of a bioadhesive and/or mucoadhesive promoting agent. WO 2008/068471 in particular discloses a formulation comprising particles of opioid agonist drug upon the surfaces of carrier particles comprising an opioid antagonist, such as naloxone.

Prior art documents, including international patent applications WO 03/005944, WO 02/067903, WO 2007/141328, WO 2010/132605, WO 01/30288 and US patent application US 2009/0263476 A1 employ pH modifying agents to promote dissolution and/or absorption of active ingredients.

We have now found that, by applying a specific formulation principle to a combination of specific active ingredients, buprenorphine and naloxone, we have provided a product with unexpected, significantly improved pharmaceutical and clinical properties.

According to a first aspect of the ~~invention~~disclosure there is provided a pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials. Such compositions are referred to hereinafter as "the compositions of the invention".

According to a second aspect of the disclosure, there is provided a process for the preparation of a sublingual tablet as defined above, which comprises directly compressing or compacting a composition as defined above.

According to a third aspect of the disclosure, there is provided a tablet suitable for sublingual administration comprising:

(a) microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising citric acid;

(b) a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof; and

(c) a disintegrant selected from the group croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.

According to a fourth aspect of the disclosure, there is provided a process for the preparation of a composition as defined above, wherein mixing takes place between microparticles of buprenorphine or salt thereof and the particles comprising weak acid or weakly-acid buffer forming materials, rendering them in associative admixture with each other.

According to a fifth aspect of the disclosure, there is provided a process for the preparation of a composition as defined above, which comprises dry mixing carrier particles with buprenorphine or salt thereof.

According to a sixth aspect of the disclosure, there is provided the use of a composition as defined above for the manufacture of a medicament for a method of treatment of opioid dependency and/or addiction.

According to a seventh aspect of the disclosure, there is provided the use of a composition as defined above for the manufacture of a medicament for a method of treatment of pain.

It is preferred that the pharmaceutical compositions comprising buprenorphine, or a pharmaceutically-acceptable salt thereof, are presented in admixture (e.g. in simple mixture) together with a disintegrant.

Claims

1. A pharmaceutical composition comprising microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising a weak acid, or particles comprising weakly-acidic buffer forming materials.

2. A composition as claimed in Claim 1, wherein the weakly acidic material comprises citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, lactic acid, acetic acid, oxalic acid, maleic acid, ammonium chloride or a combination thereof.

3. A composition as claimed in Claim 1, wherein the buffer forming materials comprise a combination of a weakly acidic material and a salt of a weakly acidic material.

4. A composition as claimed in Claim 4, wherein the weakly acidic material is as defined in Claim 3.

5. A composition as claimed in Claim 3 or Claim 4, wherein the salt is sodium citrate, potassium citrate, sodium tartrate or potassium tartrate.

6. A composition as claimed in any one of the preceding claims wherein the buffer system is citric acid/sodium citrate.

7. A composition as claimed in any one of the preceding claims which is presented as an interactive mixture comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof presented upon the surfaces of carrier particles.

8. A composition as claimed in claim 7, wherein the particles of weak acid, or of weakly-acidic buffer forming materials, are presented and act as carrier particles.

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

10. A composition as claimed in Claim 9, wherein the disintegrant is a superdisintegrant selected from croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone or a mixture thereof.

11. A composition as claimed in any one of the preceding claims, which further comprises a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof.

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

13. A process for the preparation of a sublingual tablet as defined in Claim 12, which comprises directly compressing or compacting a composition as defined in any one of Claims 1 to 11.

14. A tablet suitable for sublingual administration comprising:

(a) microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof, in associative admixture with particles comprising citric acid;

(b) a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof; and

(c) a disintegrant selected from the group croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.

15. A composition as claimed in Claim 14, which further comprises particles comprising sodium citrate.

16. A composition as claimed in any one of claims 1 to 12, 14 or 15, wherein the microparticles of buprenorphine have a weight based mean diameter of less than about 15 μm.

17. A composition as claimed in any one of claims 14 to 16, which is presented as an interactive mixture comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof presented upon the surfaces of carrier particles.

18. A composition as claimed in any one of claims Claim 7 to 12 or 17, wherein the carrier particles are of a size that is between about 100 and about 800 μm.

19. A composition as claimed in any one of claims Claim 7 to 12, 17 or 18, wherein the carrier particles are water-soluble.

20. A composition as claimed in any one of claims Claim 7 to 12, 17 to 19, wherein the carrier particles comprise mannitol.

21. A composition as claimed in any one of Claims 17 to 20, wherein the particles of weak acid, or of weakly-acidic buffer forming materials, are presented and act as carrier particles.

22. A pharmaceutical composition as claimed in any one of claims Claim 1 to 13 or 14 to 21, wherein the composition comprises particles comprising naloxone or salt thereof and disintegrant.

23. A process for the preparation of a composition as defined in any one of Claims 1 to 12 or 15 to 22, wherein mixing takes place between microparticles of buprenorphine or salt thereof and the particles comprising weak acid or weakly-acid buffer forming materials, rendering them in associative admixture with each other.

24. A process as claimed in claim 23, wherein the mixing comprises simple mixing or granulation.

25. A process for the preparation of a composition as defined in any one of Claims 7 to 12, or 17 to 22, which comprises dry mixing carrier particles with buprenorphine or salt thereof.

26. A process for the preparation of a composition as defined in Claim 22, which comprises a process as claimed in any one of Claims 23 to 25, followed by admixing with particles comprising naloxone or salt thereof and disintegrant.

27. The use of a composition as defined in any one of Claims 1 to 12 or 15 to 22 for the manufacture of a medicament for a method of treatment of opioid dependency and/or addiction.

28. The use of a composition as defined in any one of Claims 1 to 12 or 15 to 22 for the manufacture of a medicament for a method of treatment of pain.

Claims

1. A tablet suitable for sublingual administration comprising:

(a) microparticles of a pharmacologically-effective amount of buprenorphine, or a pharmaceutically-acceptable salt thereof in intimate contact with particles comprising citric acid;

(b) a pharmacologically-effective amount of naloxone, or a pharmaceutically-acceptable salt thereof; and

(c) a disintegrant selected from the group croscarmellose sodium, sodium starch glycolate, crosslinked polyvinylpyrrolidone and mixtures thereof.

2. A composition as claimed in Claim 1, wherein the microparticles of buprenorphine have a weight based mean diameter of less than about 15 μm.

3. A composition as claimed in any one of the preceding claims which is presented as an interactive mixture comprising microparticles of buprenorphine or a pharmaceutically acceptable salt thereof presented upon the surfaces of carrier particles.

4. A composition as claimed in Claim 3, wherein the carrier particles are of a size that is between about 100 and about 800 μm.

5. A composition as claimed in Claim 3 or Claim 4, wherein the carrier particles are water-soluble.

6. A composition as claimed in any one of Claims 3 to 5, wherein the carrier particles comprise mannitol.

7. A composition as claimed in any one of Claims 3 to 6, wherein the particles of citric acid are presented and act as carrier particles.

8. A pharmaceutical composition as claimed in any one of the preceding claims, wherein the composition comprises particles comprising naloxone or salt thereof and disintegrant.

9. A process for the preparation of a composition as defined in any one of the preceding claims, wherein mixing takes place between the microparticles of buprenorphine or salt thereof and the particles of citric acid, rendering them in intimate contact with each other.

10. A process as claimed in Claim 9, wherein the mixing comprises simple mixing or granulation.

11. A process for the preparation of a composition as defined in any one of Claims 3 to 8, which comprises dry mixing carrier particles with buprenorphine or salt thereof.

12. A process for the preparation of a composition as defined in Claim 8, which comprises a process as claimed in Claim 11 followed by admixing with particles comprising naloxone or salt thereof and disintegrant.

13. A method of treatment of opioid dependency and/or addiction, and/or pain, which method comprises administration of a composition as defined in any one of Claims 1 to 8 to a person suffering from, or susceptible to, the relevant condition(s).

14. A composition as defined in any one of Claims 1 to 8 for use in a method of treatment of opioid dependency and/or addiction, and/or pain.

15. The use of a composition as defined in any one of Claims 1 to 8 for the manufacture of a medicament for a method of treatment of opioid dependency and/or addiction, and/or pain.