would provide a level, or gradually tapering, drug profile, to allow gradual detox or longer term maintenance without requiring frequent administration.

Previous lipid depot formulations of buprenorphine (e.g. US 8236755) are highly effective, but provide a maximum of only around 9% buprenorphine concentration by weight. Polymeric systems, such as WO2001/154724, have been formulated with up to 20% buprenorphine but there remains scope for precursor formulations with enhanced drag loading levels.

The present inventors have now established that by appropriate choice of components, a pre-formulation comprising certain opioid active agents, particularly buprenorphine, can be formulated with a greater concentration of active agent than demonstrated hitherto while maintaining the controlled-release effect of the preparation. Certain of these precursor formulations (pre-formulations) are easy to manufacture, may be sterile-filtered, have low viscosity (allowing easy and less painful administration), allow a high bioavailability of active agent (thus allowing a smaller total amount of opioid to be used) and/or provide for effective dose control by means of control of active agent concentration and/or injection volume.

SUMMARY

In one aspect, there is provided a depot precursor formulation comprising:
a) a lipid controlled release formulation;
b) at least one oxygen containing organic solvent;
c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base;
wherein component b) comprises at least one of an amide or a sulfoxide.

In another aspect, there is provided a depot precursor formulation comprising:
a) a lipid controlled release formulation;
b) at least one oxygen containing organic solvent;
c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base;
wherein component b) comprises at least one of an amide or a sulfoxide; wherein said precursor formulation forms a depot composition upon administration to the body of a subject.

In another aspect, there is provided the use of a depot precursor formulation as defined herein in the manufacture of a medicament for the treatment or prophylaxis of:

pain,

opioid maintenance therapy or for the treatment of opioid dependence by detoxification and/or maintenance or

the symptoms of opioid withdrawal and/or cocaine withdrawal.

DETAILED DESCRIPTION

In a first aspect, the present invention thus a depot precursor formulation comprising:

a) a controlled-release matrix;

b) at least oxygen containing organic solvent;

c) at least 12% by weigh of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

Such a depot precursor will typically form a depot composition *in situ* upon administration to the body of a subject. In the case of formulations comprising a lipid controlled-release matrix, this will typically be by uptake of aqueous fluid to form a structured (e.g. liquid crystal) phase. In the case of a polymer-based controlled-release matrix component the depot will generally be formed by loss of solvent.

Suitable controlled-release matrices thus include lipid controlled release formulations (as described herein) and polymeric release matrix systems (as described herein).

Claims:

1) A depot precursor formulation comprising:

a) a lipid controlled release formulation;

b) at least one oxygen containing organic solvent;

c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base;

wherein component b) comprises at least one of an amide or a sulfoxide.

2) A depot precursor formulation comprising:

a) a lipid controlled release formulation;

b) at least one oxygen containing organic solvent;

c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base;

wherein component b) comprises at least one of an amide or a sulfoxide; wherein saidThe depot precursor formulation ~~of claim 1 which~~ forms a depot composition upon administration to the body of a subject.

3) A depot precursor formulation as claimed in claim 1 or claim 2 wherein component a) comprises:

(i) at least one of a neutral mono-acyl, di-acyl or tri-acyl lipid and/or a tocopherol; and

(ii) a phospholipid.

4) The depot precursor formulation of any preceding claim wherein the at least one active agent selected from buprenorphine and salts thereof is present at a level of greater than 30% ~~(e.g. 31 to 45%)~~ by weight buprenorphine (calculated as buprenorphine free base).

5) The depot precursor formulation of claim 4 wherein the buprenorphine and salts thereof is present at a level of 31 to 45% by weight buprenorphine (calculated as buprenorphine free base).

46) The depot precursor formulation of any preceding claim ~~1 or claim 2~~ wherein *the lipid controlled release formulation comprises an acyl glycerol* ~~(e.g. diacyl~~

~~glycerol, triacyl glycerol or mixtures thereof)~~, a phospholipid and an oxygen-containing organic solvent.

7) The depot precursor formulation of claim 6 wherein said acyl glycerol is a diacyl glycerol, a tryacyl glycerol or a mixtures thereof.

~~5~~8) The depot precursor formulation of claim ~~4~~ 6 or claim 7 wherein the lipid controlled release formulation comprises:

i) at least one neutral diacyl lipid and/or at least one tocopherol; and
ii) at least one phospholipid;

~~6~~9) The depot precursor formulation of claim ~~5~~ 8 wherein component i) comprises at least 50% by weight of components having C16 to C18 acyl groups, such groups having zero, one or two unsaturations.

~~7~~10) The depot precursor formulation of ~~any of~~ claim~~s~~ ~~5~~ 8 ~~to 6~~or claim 9 wherein component ii) comprises at least 50% of components comprising C16 to C18 acyl groups and having zero, one or two unsaturations.

~~8~~11) The depot precursor formulation of any preceding claim wherein component b) comprises at least one solvent selected from alcohols, ketones, esters (including lactones), ethers, amides (including lactams) and sulphoxides.

~~9~~12) The depot precursor formulation of any preceding claim wherein component b) comprises NMP.

~~10~~13) The depot precursor formulation of any preceding claim wherein component b) comprises dimethylsulfoxide.

~~11~~14) The depot precursor formulation of any preceding claim wherein component c) comprises buprenorphine as the free base.

~~12~~15) The depot precursor formulation of any preceding claim for once-monthly administration.

~~13~~16) The depot precursor formulation of any preceding claim having a dose in the range 10 to 200 mg buprenorphine (calculated as free base) ~~particularly 20 to 200mg, more preferably 40 to 140mg~~.

17) The depot precursor formulation of any preceding claim having a dose in the range 20 to 200mg buprenorphine (calculated as free base).

18) The depot precursor formulation of any preceding claim having a dose in the range 40 to 140mg buprenorphine (calculated as free base).

~~14~~19) The depot precursor formulation of any preceding claim wherein the precursor formulation is in ready-to-administer form.

~~15~~20) The depot precursor formulation of any preceding claim wherein the precursor formulation is stable to storage in ready-to-administer form.

~~16~~21) The depot precursor formulation of any preceding claim containing 25% or greater ~~and most preferably greater than 30%~~ by weight buprenorphine (calculated as buprenorphine free base).

22) The depot precursor formulation of any preceding claim containing greater than 30% by weight buprenorphine (calculated as buprenorphine free base).

~~17~~23) The depot precursor formulation of any preceding claim in ready-to-administer form.

24) A depot precursor formulation of any preceding claim which is dispensable through a 23 gauge (22 AWG / 0.635 mm diameter) needle by manual pressure.

25) A depot precursor formulation as claimed in any of claims 1 to 23 having a viscosity of 1 to 1000 mPas at 20^0C.

26) A depot precursor formulation of any preceding claim comprising:
15 – 25 wt.% glycerol dioleate (GDO);
10 – 25 wt.% phosphatidylcholine (PC);
20 – 35 wt.% solvent selected from the group consisting of alcohols, ketones, ethers, amides, sulphoxides, and mixtures thereof; and
at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

27) A depot precursor formulation as claimed in claim 26 comprising:
15 – 25 wt.% glycerol dioleate (GDO);
10 – 25 wt.% phosphatidylcholine (PC);
20 – 35 wt.% N-methyl-2-pyrrolidone (NMP); and
at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

28) A depot precursor formulation as claimed in claim 26 comprising:
15 – 25 wt.% glycerol dioleate (GDO);
10 – 25 wt.% phosphatidylcholine (PC);
20 – 35 wt.% N-methyl-2-pyrrolidone (NMP); and
at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base;
wherein the dose of buprenorphine (calculated as buprenorphine free base) is 20 to 200mg.

29) The use of a depot precursor formulation as claimed in any one of claims 1 to 28 in the manufacture of a medicament for the treatment or prophylaxis of:

pain,

opioid maintenance therapy or for the treatment of opioid dependence by detoxification and/or maintenance or

the symptoms of opioid withdrawal and/or cocaine withdrawal.

~~18) A depot composition formed by administration to a (preferably human) subject of a depot precursor formulation of any preceding claim.~~

19) The depot composition of claim 18 which provides a Cmax (maximum concentration) in the blood plasma of said subject after a single administration of no more than 0.3 ng/ml per mg of administered buprenorphine, preferably no more than 0.17 ng/ml per mg of administered buprenorphine

20) The depot composition of claim 19 or claim 20 which, upon administration to said subject provides linearity (proportionality) of the AUC dose in comparison with the administered dose of buprenorphine.

21) The depot composition of any of claims 18 to 20 which, upon administration to said subject provides a buprenorphine blood plasma profile not having any lag phase.

22) The depot composition of any of claims 18 to 21 wherein, following administration to said subject of a precursor formulation of any of claims 1 to 17 once monthly for at least 6 months, Cmin and Cmax at a steady-state both fall with the range of between 0.4 ng/mL and 10 ng/mL.

23) The depot composition of any of claims 18 to 21 wherein, following administration to said subject of a precursor formulation of any of claims 1 to 17 once monthly for at least 6 months, Cmin and Cmax at a steady-state both fall with the range of between 0.2 ng/mL and 2 ng/mL.

24) The depot composition of any of claims 18 to 23 which comprises:

a) a lipid controlled release formulation;
b) optionally at least oxygen containing organic solvent;
c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof;
d) at least one aqueous fluid.

25) A method of sustained delivery of buprenorphine to a human or non-human animal body, said method comprising administering a depot precursor formulation comprising:
a) a lipid controlled release formulation;

b) at least one oxygen-containing organic solvent selected from at least one of an amide or a sulfoxide;

c) at least 21% of at least one active agent selected from buprenorphine and salts thereof.

26) A method for the formation of a depot composition comprising exposing a precursor formulation comprising:

a) a lipid controlled-release formulation;

b) at least one oxygen-containing organic solvent selected from at least one of an amide or a sulfoxide;

c) at least 21% by weight of at least one active agent selected from buprenorphine and salts thereof;

to an aqueous fluid *in vivo*.

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27) A method of treatment or prophylaxis of a human or non-human animal subject comprising administration of a precursor formulation of any of claims 1 to 17.

28) A method of claim 27 for the treatment of pain, for opioid maintenance therapy or for the treatment of opioid dependence by detoxification and/or maintenance or for the treatment or prophylaxis of the symptoms of opioid withdrawal and/or cocaine withdrawal.

29) A method of transitioning of a subject from daily sublingual buprenorphine to a sustained buprenorphine formulation, comprising administering to said subject a monthly buprenorphine depot precursor formulation according to any of claims 1 to 17, comprising 0.5 to 3 times his previous daily buprenorphine dose.