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.

The present disclosure provides 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.

In one aspect, the present disclosure refers to a depot precursor formulation comprising:

a) a controlled-release polymer matrix;

b) at least oxygen containing organic solvent, comprising an amide solvent; and

c) greater than 30% by weight 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).

The high-loading depot precursor formulations of the present disclosure (as well as the other corresponding examples) will typically comprise greater than 15% (e.g. 15 to 50%) by weight of active agent, preferably at least 21% and more preferably at least 25% by weight. Greater than 30% by weight is particularly preferred. Active agents will generally be buprenorphine or salts thereof as indicated herein.

The present disclosure also provides a depot composition formed or formable from any of the depot precursor formulations described herein. Such a depot composition may comprise:

a) a controlled-release matrix;
b) optionally at least one oxygen containing organic solvent;
c) at least 12% of at least one active agent selected from buprenorphine and salts thereof
d) optionally at least one aqueous fluid.

Such a depot composition will typically be formed upon exposure of a precursor formulation of the present disclosure (such as any precursor formulation in any embodiment or preferred embodiment described herein) to an aqueous fluid *in vivo*. Exposure to such an aqueous fluid will generally result in a loss of solvent and/or an addition of water to the precursor formulation and may result in a phase change such as from solution to solid (a precipitation) or from a low-viscosity phase, such as a solution or L_2 phase to a high viscosity phase such as a liquid crystalline phase.

The disclosure also provides 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 controlled-release matrix;
b) at least oxygen containing organic solvent;
c) at least 12% of at leastone active agent selected from buprenorphine and salts thereof.

Preferably, the precursor formulation (pre-formulation) administered in such a method is a pre-formulation of the disclosure as described herein.

The method of administration suitable for the above method of the disclosure will be a method appropriate for the condition to be treated or addressed. A parenteral depot will thus be formed by parenteral (e.g. subcutaneous or intramuscular) administration. A bioadhesive non-parenteral (e.g. topical) depot composition may be formed by administration to the surface of skin, mucous membranes and/or nails, to ophthalmological, nasal, oral or internal surfaces or to cavities such as nasal, rectal, vaginal or buccal cavities, the periodontal pocket or cavities formed following extraction of a natural or implanted structure or prior to insertion of an implant (e.g a joint, stent, cosmetic implant, tooth, tooth filling or other implant).

Since the key medicinal properties of opioids are analgesia and use in detoxification and/or maintenance from opioid dependence, the formulations will typically be for systemic absorption, although topical pain relief can be provided by opioids and they are additionally of value in cough suppression (especially codeine and hydrocodone), diarrhoea suppression, anxiety due to shortness of breath (especially oxymorphone) and antidepression (especially buprenorphine). For these, appropriate administration methods, such as bioadhesive pain-relieving gels for topical pain, or non-absorbed oral compositions for diarrhoea suppression may be used.

The present disclosure also provides a method for the formation of a depot composition comprising exposing a precursor formulation comprising:

a) a controlled-release matrix;

b) at least oxygen containing organic solvent;

c) at least 12% by weight of at least one active agent selected from buprenorphine and salts thereof.

to an aqueous fluid *in vivo*.

Suitable aqueous fluids are particularly body fluids as indicated herein. Preferably the pre-formulation administered is a pre-formulation of the present disclosure as described herein and more preferably a preferred formulation according to the present disclosure. The exposure to a fluid "in vivo" may evidently be internally within the body or a body cavity, or may be at a body surface such as a skin surface, depending upon the nature of the composition.

The present disclosure also provides a process for the formation of a precursor formulation suitable for the administration of an opioid bioactive agent to a (preferably mammalian) subject, said process comprising forming a mixture of

a) a controlled-release matrix; and

b) at least one oxygen containing organic solvent;

and dissolving or dispersing at least 12% by weight of at least one buprenorphine in the mixture, or in at least one of components a, or b prior to forming the low viscosity mixture. Preferably the pre-formulation so-formed is a formulation of the disclosure as described herein. The process may additionally comprise sterilisation, such as by sterile filtration.

The present disclosure additionally provides for a method of treatment or prophylaxis of a human or non-human animal subject comprising administration of a precursor formulation as described herein. Such a method may be for the treatment of pain or for the treatment of drug dependence (typically opioid dependence) by detoxification and/or maintenance as described herein.

In another aspect, the present disclosure refers to the precursor formulation as described herein for use in 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.

In another aspect, the present disclosure refers to the precursor formulation as described herein for use to transition a subject from daily sublingual buprenorphine to a sustained buprenorphine formulation wherein said subject is to be administered a monthly buprenorphine depot precursor formulation comprising 0.5 to 3 times his previous daily buprenorphine dose.

In another aspect, the present disclosure refers to the use of the precursor formulation as described herein in the manufacture of a medicament 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.

As used herein, the term "low viscosity mixture" is used to indicate a mixture which may be readily administered to a subject and in particular readily administered by means of a standard syringe and needle arrangement. This may be indicated, for example by the ability to be dispensed from a 1 ml disposable syringe through a 23 gauge (22 AWG / 0.635 mm diameter) needle by manual pressure. In a further preferred embodiment, the low viscosity mixture should be a mixture capable of passing through a standard sterile filtration membrane such as a 0.22 μm syringe filter. In other preferred embodiments, a similar functional definition of a suitable viscosity can be defined as the viscosity of a pre-formulation that can be sprayed using a compression pump or pressurized spray device using conventional spray equipment. A typical range of suitable viscosities would be, for example, 0.1 to 5000 mPas, preferably 1 to 1000mPas at 20°C (e.g. 10 to 1000 mPas or 50 to 1000 mPas at 20°C).

It has been observed that by the addition of small amounts of low viscosity solvent, as indicated herein, a very significant change in viscosity can be provided, particularly for lipid formulations (as described herein). As indicated in Example 11 below, for example, the addition of only 5% solvent (in the case of Example 11, ethanol) can reduce viscosity of a lipid mixture by several orders of magnitude.

Claims:

1) A depot precursor formulation comprising:
a) a controlled-release polymer matrix;
b) at least oxygen containing organic solvent, comprising an amide solvent; and
c) greater than 30% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

2) The depot precursor formulation of claim 1 wherein the polymer matrix comprises at least one biodegradable polymer.

3) The depot precursor formulation of claim 2 wherein the biodegradable polymer comprises a polyester and/or polyamide, such as at least one of polylactate, polyglycolate, and/or polylactate/glycolate copolymers.

4) The depot precursor formulation of any of claims 1 to 3 wherein the polymer matrix comprises homopolymers, copolymers, or mixtures of homopolymers and copolymers.

5) The depot precursor formulation of any of claims 1 to 4 wherein the polymer is in the form of a molecular solution.

6) The depot precursor formulation of any of claims 1 to 4 wherein the polymer is in the form of microspheres in suspension.

7) The depot precursor formulation of any of claims 1 to 6 wherein the controlled release matrix comprises PLGA microspheres.

8) The depot precursor formulation of any of claims 1 to 7 wherein component c) is present at a level of 31 to 55% by weight buprenorphine (calculated as buprenorphine free base).

9) The depot precursor formulation of claim 8 wherein component c) is present at a level of 31 to 45% by weight buprenorphine (calculated as buprenorphine free base).

10) The depot precursor formulation of any of claims 1 to 9 comprising 40 to 70% by weight component b).

11) The depot precursor formulation of any of claims 1 to 10 wherein component b) comprises at least one of N-methyl-2-pyrrolidone (NMP), dimethyl formamide (DMF) and dimethyl acetamide (DMA).

12) The depot precursor formulation of claim 11 wherein component b) comprises N-methyl-2-pyrrolidone (NMP).

13) The depot precursor formulation of any of claims 1 to 12 for once-monthly administration.

14) The depot precursor formulation of any of claims 1 to 13 having a dose in the range 10 to 200 mg buprenorphine (calculated as free base).

15) The depot precursor formulation of claim 14 having a dose in the range 20 to 200 mg buprenorphine (calculated as free base).

16) The depot precursor formulation of claim 14 having a dose in the range 40 to 140 mg buprenorphine (calculated as free base).

17) The depot precursor formulation of any of claims 1 to 16 in ready-to-administer form.

18) The precursor formulation of any of claims 1 to 17 for use in 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.

19) The precursor formulation of any of claims 1 to 17 for use to transition a subject from daily sublingual buprenorphine to a sustained buprenorphine formulation wherein said subject is to be administered a monthly buprenorphine depot precursor formulation comprising 0.5 to 3 times his previous daily buprenorphine dose.

20) The use of the precursor formulation of any of claims 1 to 17 in the manufacture of a medicament 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.