desirable release profile when the buprenorphine concentration is held above around 16% by weight.

Summary

The present disclosure provides an injectable liquid formulation comprising:

a) a lipid controlled-release matrix comprising at least 50% triacyl lipids;

b) at least one oxygen containing organic solvent;

c) at least 16% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

Preferred triacyl lipids in all aspects and embodiments of the present disclosure are triacyl glycerols (triglycerides).

In one aspect, there is provided an injectable liquid formulation comprising:

a) a lipid controlled-release matrix comprising at least 50% triacyl lipids and optionally comprising phospholipid(s);

b) at least one oxygen containing organic solvent;

c) 16% to 60% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base; and

wherein the ratio of triacyl lipid(s) : phospholipid(s) (w/w) in the lipid controlled-release matrix a) is in the range of 90:10 to 100:0.

Such injectable liquid formulations as described herein in all aspects and embodiments of the disclosure typically form a controlled-release composition upon administration to the body of a subject. Such a subject may be a human or animal subject such as any of those described herein.

The injectable liquid formulations described herein in all aspects and embodiments of the disclosure typically have at least one active agent selected from buprenorphine and salts thereof present at a level of greater than 21% (e.g. greater than 30%, such as 31 to 50%) by weight buprenorphine. Herein throughout, all percentages of buprenorphine are calculated by weight as percentage of buprenorphine free base in the complete formulation, unless otherwise stated.

The injectable liquid formulations of the disclosure may be administered to a suitable subject, particularly a mammalian subject in thereby form a controlled-release formulation. The present disclosure therefore provides a controlled-release composition formed by administration to a (preferably human) subject of an injectable liquid formulation as described in any of the aspects or embodiments disclosed herein. Evidently, preferred formulations of the disclosure will result in preferred controlled-release compositions.

The controlled-release compositions of the disclosure show advantageous release profiles, particularly with regard to maintaining plasma concentrations of buprenorphine within a

functional window for an extended period. Thus, following administration to said subject of an injectable liquid (as described in any embodiment herein) once monthly for at least 6 months, Cmin and Cmax (particularly the mean of each, taken in a population of subjects typically comprising at least at least 10 subjects) at a steady-state both fall with the range of between 0.2 ng/mL to 12 ng/mL, preferably 0.4 ng/mL and 15 ng/mL.

The disclosure also provides a method of sustained delivery of buprenorphine to a human or non-human animal body, said method comprising administering an injectable liquid formulation comprising:

a) a lipid controlled-release matrix comprising at least 50% triacyl lipids;

b) at least one oxygen containing organic solvent;

c) at least 16% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base.

Such formulations and compositions of the present disclosure can be used in the treatment of any indication for which the chronic administration of buprenorphine is suitable. The disclosure thus provides a method of treatment or prophylaxis of a human or non-human animal subject comprising administration of an injectable liquid formulation as described in any aspect or embodiment of the disclosure.

In another aspect, there is provided an injectable liquid formulation as described herein for use in a method of treatment or prophylaxis of a human or non-human animal subject.

Such a method may be for the treatment or prophylaxis of any suitable condition, including 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.

Correspondingly, the present disclosure provides an injectable liquid formulation or controlled-release composition as described herein for use in therapy. Such therapy may be for the treatment or prophylaxis of any suitable condition, including 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.

In another aspect, there is provided use of:

a) a lipid controlled-release matrix comprising at least 50% triacyl lipids and optionally comprising phospholipid(s);

b) at least one oxygen containing organic solvent;

c) 16% to 60% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base; and

wherein the ratio of triacyl lipid(s) : phospholipid(s) (w/w) in the lipid controlled-release matrix a) is in the range of 90:10 to 100:0;

in the preparation of an injectable liquid formulation for treatment of pain, opioid maintenance therapy, or opioid dependence by detoxification and/or maintenance or for treatment or prophylaxis of the symptoms of opioid withdrawal and/or cocaine withdrawal.

Detailed Description of the Invention

Highly effective lipid-based controlled-release formulations have been disclosed over the last few years, including formulations such as those of WO2005/117830 which comprise diacyl lipids and phospholipids in appropriate mixtures so as to generate formulations which

Claims:

1) An injectable liquid formulation comprising:

a) a lipid controlled-release matrix comprising at least 50% triacyl lipids and optionally comprising phospholipid(s);

b) at least one oxygen containing organic solvent;

c) 16% to 60% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base; and

wherein the ratio of triacyl lipid(s) : phospholipid(s) (w/w) in the lipid controlled-release matrix a) is in the range of 90:10 to 100:0.

2) The injectable liquid formulation of claim 1 comprising greater than 30% by weight buprenorphine or salts thereof (calculated as buprenorphine free base).

3) The injectable liquid formulation of claim 1 or claim 2 wherein component a) forms 10% to 60% of the total formulation.

4) The injectable liquid formulation of any preceding claim wherein component a) comprises at least 50% triglycerides.

5) The injectable liquid formulation of any preceding claim wherein component a) comprises at least 60% triglycerides.

6) The injectable liquid formulation of any preceding claim wherein component a) comprises at least 80% triglycerides.

7) The injectable liquid formulation of any preceding claim wherein the lipid controlled release formulation further comprises:

i) at least one neutral diacyl lipid

ii) at least one tocopherol; and/or

iii) at least one phospholipid;

8) The injectable liquid formulation of any preceding claim wherein component b) is present at 15 to 50% by weight of the formulation.

9) The injectable liquid formulation of any preceding claim wherein component b) comprises at least one amide and/or at least one sulphoxide.

10) The injectable liquid formulation of any preceding claim wherein component b) comprises N-methyl-2-pyrrolidone (NMP), dimethylsulfoxide (DMSO) or mixtures thereof.

11) The injectable liquid formulation of any preceding claim having a dose in the range 20 to 600 mg buprenorphine (calculated as free base).

12) The injectable liquid formulation of any preceding claim having a dose in the range 20 to 240 mg buprenorphine (calculated as free base) per month of release duration and having a release duration of 1 to 4 months.

13) The injectable liquid formulation of any preceding claim wherein the formulation is in ready-to-administer form.

14) The injectable liquid formulation of any preceding claim having a viscosity of 20 to 600 mPas at 20°C.

15) The injectable liquid formulation of any preceding claim wherein the ratio of triacyl lipid(s) : phospholipid(s) (w/w) in the lipid controlled-release matrix a) is in the range of 95:5 to 100:0.

16) The injectable liquid formulation of any preceding claim wherein the level of phospholipid in the formulation as a whole is less than 8 wt.%.

17) The injectable liquid formulation of any preceding claim wherein the level of phospholipid in the formulation as a whole is 6 wt% or less.

18) The injectable liquid formulation of any preceding claim wherein the level of phospholipid in the formulation as a whole is 4 wt% or less.

19) An injectable liquid formulation as claimed in any of claims 1 to 18 for use in a method of treatment or prophylaxis of a human or non-human animal subject.

20) An injectable liquid formulation as claimed in any of claims 1 to 18 for use according to claim 19, wherein said use is:
a method of treatment of pain;
a method of treatment for opioid maintenance therapy;
or a method of treatment of opioid dependence by detoxification and/or maintenance; or a method of treatment or prophylaxis of the symptoms of opioid withdrawal and/or cocaine withdrawal.

21) Use of:
a) a lipid controlled-release matrix comprising at least 50% triacyl lipids and optionally comprising phospholipid(s);
b) at least one oxygen containing organic solvent;

c) 16% to 60% by weight of at least one active agent selected from buprenorphine and salts thereof, calculated as buprenorphine free base; and

wherein the ratio of triacyl lipid(s) : phospholipid(s) (w/w) in the lipid controlled-release matrix a) is in the range of 90:10 to 100:0;

in the preparation of an injectable liquid formulation for treatment of pain, opioid maintenance therapy, or opioid dependence by detoxification and/or maintenance or for treatment or prophylaxis of the symptoms of opioid withdrawal and/or cocaine withdrawal.