if this system could be simplified, and in particular if it could be made effective in the absence of bioactive agents or other "crystal hardeners".

The present inventors have now established that by providing a pre-formulation comprising at least one fatty acid ester of a sugar or sugar derivative, at least one phospholipid (such as phosphatidyl choline or phosphatidyl ethanolamine), at least one biocompatible, oxygen containing, low viscosity organic solvent in carefully controlled proportions, a pre-formulation may be generated which provides a complementary system to known depot formulations based on the combination of diacylglycerols and phospholipids, without the need for an additional crystal hardener component. By use of specific components in carefully selected ratios a depot formulation can be generated having a combination of properties matching or exceeding the performance of known sorbitan-based lipid controlled-release compositions.

In particular, the pre-formulation shows an acceptable release profile, is easy to manufacture, may be sterile-filtered, has sufficiently low viscosity (allowing administration through a typical needle), allows a high level of bioactive agent to be incorporated (thus potentially allowing a smaller amount of composition and/or active agent to be used), requires shallow injection and/or forms a desired non-lamellar depot composition *in vivo* having a "non-burst" release profile. The compositions can be administered by i.m., or s.c. and are suitable for self-administration.

Advantages of the compositions of the present invention over polymer formulations, such as PLGA spheres, include the ease of manufacture (including sterilization), handling and use properties combined with low initial release ("non-burst profile") of active agent.

Summary

The disclosure provides a pre-formulation comprising a low viscosity, non-liquid crystalline, mixture of:

i) at least one ester of a sugar or sugar derivative;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and wherein the pre-formulation forms, or is capable of forming, at least one non-lamellar liquid crystalline phase structure upon contact with an aqueous fluid; with the proviso that the pre-formulation does not further comprise a liquid crystal hardener.

In one aspect, there is provided a pre-formulation comprising a low viscosity, non-liquid crystalline, mixture of:

i) at least one sorbitan ester;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein component iii) comprises or consists of ethanol, DMSO, NMP or mixtures thereof;

wherein the pre-formulation forms, or is capable of forming, at least one non-lamellar liquid crystalline phase structure upon contact with an aqueous fluid; and wherein the pre-formulation does not further comprise triglyerides, retinyl palmitate, benzyl benzoate, cholesterol, ubiquinone, tocopherols or mixtures thereof.

Generally, the aqueous fluid will be a body fluid such as fluid from a mucosal surface, tears, sweat, saliva, gastro-intestinal fluid, extra-vascular fluid, extracellular fluid, interstitial fluid or plasma, and the pre-formulation will form a liquid crystalline phase structure when contacted with a body surface, area or cavity (e.g. *in vivo*) upon contact with the aqueous body fluid. The pre-formulation of the disclosure may optionally contain a certain amount of water prior to administration, but this will not be sufficient to lead to the formation of the necessary liquid crystalline phase prior to administration.

The disclosure further provides a pharmaceutical formulation comprising the pre-formulation of the first embodiment, which may additionally comprise at least one pharmaceutically tolerable carrier, preservative, excipient or other pharmaceutically tolerable component.

The disclosure also provides a depot composition formed by exposing the pre-formulation as defined herein or the pharmaceutical formulation as defined herein to an aqueous fluid *in vivo* following administration.

The disclosure further provides a method of delivery of a bioactive agent to a human or non-human animal (preferably mammalian) body, this method comprising administering a pre-formulation comprising a non-liquid crystalline, low viscosity mixture of:

i) at least one ester of a sugar or sugar derivative;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture and wherein the pre-formulation does not further comprise a liquid crystal hardener, whereby to form at least one non-lamellar liquid crystalline phase structure upon contact with an aqueous fluid *in vivo* following administration.

Additionally, the disclosure provides a process for the formation of a pre-formulation as defined herein, suitable for the administration of a bioactive agent to a (preferably mammalian) subject, said process comprising forming a non-liquid crystalline, low viscosity mixture of

i) at least one ester of a sugar or sugar derivative;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

and dissolving or dispersing at least one bioactive agent in the low viscosity mixture, or in at least one of components i), ii) or iii) prior to forming the low viscosity mixture wherein the pre-formulation does not further comprise a liquid crystal hardener.

The disclosure also provides the use of a non-liquid crystalline, low viscosity mixture of:

i) at least one ester of a sugar or sugar derivative;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein at least one bioactive agent is dissolved or dispersed in the low viscosity mixture in the manufacture of a pre-formulation for use in the sustained delivery of said active agent, wherein said pre-formulation is capable of forming at least one non-lamellar liquid crystalline phase structure upon contact with an aqueous fluid and wherein the pre-formulation does not further comprise a liquid crystal hardener.

The disclosure further provides a method of treatment or prophylaxis of a human or non-human (preferably mammalian) animal subject comprising administration of a pre-formulation as defined herein.

In another aspect, there is provided a pre-formulation as defined herein for use in the treatment or prophylaxis of a disease.

In another aspect, there is provided a pre-filled administration device containing a pre-formulation as defined herein.

In another aspect, there is provided a kit comprising an administration device as hereinbefore defined.

Additionally, the disclosure provides a method of delivery of a pre-formulation to a subject in need thereof, the method involving administering a pre-

formulation as defined herein using an administration as defined herein.

Detailed description of the Invention

Formulations of the present invention generate a non-lamellar liquid crystalline phase following administration. Formulations of the invention differ from known lipid systems based on glycerol dioleate and phosphatidyl choline (GDO/PC) in that the glycerol-derived diacyl lipid is replaced, largely replaced or at least supplemented with an ester of a sugar or sugar derivative.

WO2013/032207 A1 discloses pre-formulations comprising a fatty acid sorbitan ester, a phospholipid, a liquid crystal hardener and ethanol. The compositions described therein are disclosed as being suitable for slow release of active agents. Further data for the slow-release of leuprolide is given by the same authors in *J. Controlled Release* 185 (2014), 62-70. In WO2013/032207 the role of the liquid crystal hardener is indicated as being essential to increasing the curvature of the non-lamellar phase. The liquid crystal hardener is disclosed in this publication as a compound being free of an ionizable group, having a hydrophobic moiety of 15 to 40 carbon atoms and having a triacyl group or a carbon ring structure. Specific Examples include triglycerides, retinyl palmitate, tocopherol acetate, cholesterol, benzyl benzoate, and mixtures thereof. The same liquid crystal hardeners are employed in the formulations of WO2014/104784 A1, WO2014/104788 A1 and WO2014/104791 A1. Ubiquinone is additionally suggested as a liquid crystal hardener in these publications.

The presence of a liquid crystal hardener is required in the above-mentioned controlled-release systems based on sorbitan-ester and phospholipid. The clear disclosure of WO2013/032207, WO2014/104784, WO2014/104788 and WO2014/104791 is that sorbitan esters and phospholipids cannot be formulated together in such a way as to produce an effective slow-release lipid formulation, without the addition presence of this liquid crystal hardener.

The present inventors have now established that useful slow-release compositions can be provided by the combination of at least one sorbitan ester with at least one phospholipid, in the absence of an additional liquid crystal hardener. Specifically, it

CLAIMS:

1. A pre-formulation comprising a low viscosity, non-liquid crystalline, mixture of:

i) at least one sorbitan ester;

ii) at least one phospholipid;

iii) at least one biocompatible, oxygen containing, low viscosity organic solvent;

wherein component iii) comprises or consists of ethanol, DMSO, NMP or mixtures thereof;

wherein the pre-formulation forms, or is capable of forming, at least one non-lamellar liquid crystalline phase structure upon contact with an aqueous fluid;

and wherein the pre-formulation does not further comprise triglyerides, retinyl palmitate, benzyl benzoate, cholesterol, ubiquinone, tocopherols or mixtures thereof.

2. A pre-formulation according to claim 1 which does not comprise any component free of an ionizable group, having a hydrophobic moiety of 15 to 40 carbon atoms with a triacyl group or a carbon ring structure.

3. A pre-formulation according to claim 1 or claim 2 wherein component i) comprises at least one fatty acid ester of a sorbitan comprising a sorbitan head group and one to three fatty acyl tail groups.

4. A pre-formulation as claimed in claim 3 wherein component i) comprises at least one fatty acid sorbitan di-ester comprising a sorbitan head group and two fatty acyl tail groups.

5. A pre-formulation according to claim 3 or claim 4 wherein each fatty acyl tail group is independently selected from caproic, caprylic, capric, lauric, myristic,

palmitic, phytanic, palmitolic, stearic, iso-stearic, oleic, elaidic, linoleic, linolenic, arachidonic, behenic or lignoceric acids.

6. A pre-formulation according to claim 3 or claim 4 wherein each fatty acyl tail group is oleic acid.

7. A pre-formulation according to any one of the preceding claims wherein component ii) is at least one phosphatidyl choline or at least one phosphatidyl ethanolamine or mixtures thereof.

8. A pre-formulation according to any one of the preceding claims wherein the weight ratio of i) : ii) is in the range of 30:70 to 80:20.

9. A pre-formulation according to claim 8 wherein component i) comprises at least 30% fatty acid di-esters of sorbitan and component ii) is soy phosphatidylcholine, wherein the weight ratio of i) : ii) is 45:55 to 75:25.

10. A pre-formulation according to any one of the preceding claims having a viscosity of below 1000 mPas at 20°C.

11. A pre-formulation according to any one of the preceding claims further comprising at least one active agent.

12. A pre-formulation according to claim 11 wherein said active agent is a peptide active agent.

13. A pre-formulation as claimed in claim 11 or claim 12 wherein said active agent is selected from opioid agonists, opioid antagonists, GnRH agonists, GnRH antagonists, somatostatins and somatostatin receptor (SSTR) agonists, glucagon-like peptide 1 (GLP-1) receptor agonists, and glucagon-like peptide 2 agonists, and mixtures thereof.

14. A pre-formulation according to claim 11 wherein the active agent is an opioid agonist selected from buprenorphine, fentanyl, sufentanil, remifentanil, oxymorphone, dimorphone, dihydroetorphine or diacetylmorphine; or wherein the active agent is an opioid antagonist selected from naloxone, nalmefene or naltrexone.

15. A pre-formulation according to claim 11 wherein said active agent is a cyclic peptide of 30 or fewer amino acids.

16. A pre-formulation as claimed in any one of claims 1 to 15 for use in the treatment or prophylaxis of a disease.

17. A pre-filled administration device containing a pre-formulation as claimed in any one of claims 1 to 15.

18. A kit comprising an administration device as claimed in claim 17.