(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 July 2014 (03.07.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/104784 A4

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 9/06* (2006.01)
A61K 9/08 (2006.01) *A61K 47/30* (2006.01)

(21) International Application Number:
PCT/KR2013/012259

(22) International Filing Date:
27 December 2013 (27.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10-2012-0157562
28 December 2012 (28.12.2012) KR

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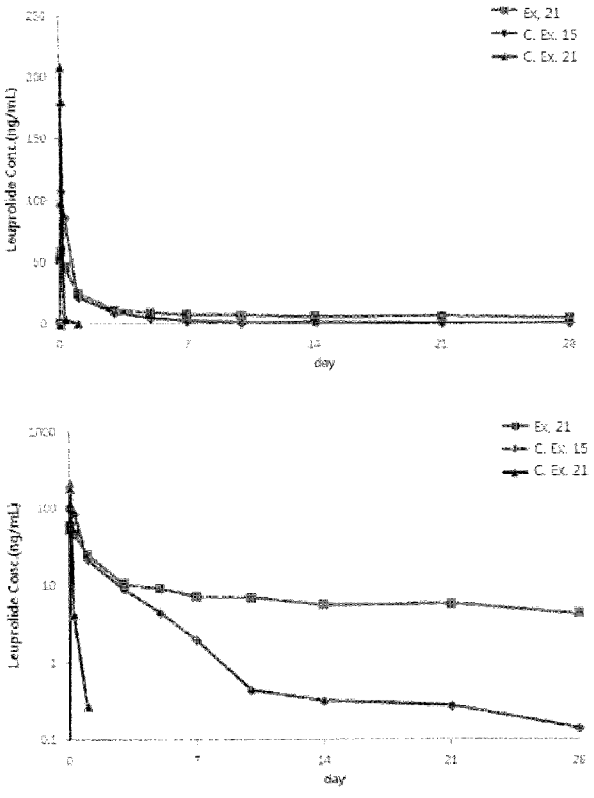
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,

[Continued on next page]

(54) Title: SUSTAINED-RELEASE LIPID PRE-CONCENTRATE OF CATIONIC PHARMACOLOGICALLY ACTIVE SUBSTANCE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

[Fig. 3]



(57) Abstract: Disclosed is a sustained-release lipid pre-concentrate, comprising: a) at least one liquid crystal former; b) at least one neutral phospholipid; c) at least one liquid crystal hardener; and d) at least one anionic anchoring agent, wherein the sustained-release pre-concentrate exists as a lipid liquid phase in the absence of aqueous fluid and forms into a liquid crystal upon exposure to aqueous fluid. The sustained-release lipid pre-concentrate is configured to enhance the sustained release of cationic pharmacologically active substance through ionic interaction between the anionic anchoring agent and the cationic pharmacologically active substance.

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HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with amended claims (Art. 19(1))*

Date of publication of the amended claims: 31 July 2014

AMENDED CLAIMS
received by the International Bureau on 26 June 2014 (26.06.2014)

CLAIMS

1. A sustained-release lipid pre-concentrate, comprising:

a) at least one sorbitan unsaturated fatty acid ester having two or more -OH (hydroxyl) groups in the polar head;

b) at least one neutral phospholipid;

c) at least one liquid crystal hardener; and

d) at least one anionic anchoring agent,

wherein the sustained-release pre-concentrate exists as a lipid liquid phase in the absence of aqueous fluid and forms into a liquid crystal upon exposure to aqueous fluid.

2. The sustained-release lipid pre-concentrate of claim 1, wherein the sorbitan unsaturated fatty acid ester is selected from the group consisting of sorbitan monooleate, sorbitan monolinoleate, sorbitan monopalmitoleate, sorbitan monomyristoleate, sorbitan sesquioleate, sorbitan sesquilinoleate, sorbitan sesquipalmitoleate, sorbitan sesquimyristoleate, sorbitan dioleate, sorbitan dilinoleate, sorbitan dipalmitoleate, sorbitan dimyristoleate, and a combination thereof.

3. The sustained-release lipid pre-concentrate of claim 1, wherein the sorbitan unsaturated fatty acid ester is selected from the group consisting of sorbitan monooleate, sorbitan monolinoleate, sorbitan monopalmitoleate, sorbitan monomyristoleate, sorbitan sesquioleate, and a combination

thereof.

4. The sustained-release lipid pre-concentrate of claim 1, wherein the neutral phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, sphingomyelin, and a combination thereof, having saturated or unsaturated alkyl ester group of 4 to 30 carbon atoms.

5. The sustained-release lipid pre-concentrate of claim 1, wherein the liquid crystal hardener is free of an ionizable group and its hydrophobic moiety has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure.

6. The sustained-release lipid pre-concentrate of claim 1, wherein the liquid crystal hardener is selected from the group consisting of triglyceride, retinyl palmitate, tocopherol acetate, cholesterol, benzyl benzoate, ubiquinone, and a combination thereof.

7. The sustained-release lipid pre-concentrate of claim 1, wherein the liquid crystal hardener is selected from the group consisting of tocopherol acetate, cholesterol, and a combination thereof.

8. The sustained-release lipid pre-concentrate of claim 1,

wherein the anionic anchoring agent comprises a polar head and a hydrophobic moiety, said polar head containing at least one selected from the group consisting of a carboxylate, a phosphate, a sulfate or a sulfonate, said hydrophobic moiety containing 4 to 40 carbon atoms.

9. The sustained-release lipid pre-concentrate of claim 8, wherein the anionic anchoring agent with the carboxylate in the polar head is selected from the group consisting of palmitic acid, palmitoleic acid, lauric acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, myristic acid, myristoleic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, linolenic acid, alpha-linolenic acid(ALA), eicosapentaenoic acid(EPA), docosahexaenoic acid(DHA), linoleic acid(LA), gamma-linoleic acid(GLA), dihomo gamma-linoleic acid(DGLA), arachidonic acid(AA), oleic acid, vaccenic acid, elaidic acid, eicosanoic acid, erucic acid, nervonic acid, benzoic acid, sorbic acid, pamoic acid, lipoic acid, and a combination thereof.

10. The sustained-release lipid pre-concentrate of claim 8, wherein the anionic anchoring agent with the carboxylate in the polar head is selected from the group consisting of caprylic acid, capric acid, stearic acid, oleic acid, linolenic acid, benzoic acid, sorbic acid, lipoic acid, and a combination thereof.

11. The sustained-release lipid pre-concentrate of claim 8, wherein the anionic anchoring agent with the phosphate in the polar head is selected from the group consisting of phosphatidyl serine, phosphatidyl glycerine, phosphatidic acid, and a combination thereof.

12. The sustained-release lipid pre-concentrate of claim 8, wherein the anionic anchoring agent with the sulfate in the polar head is selected from the group consisting of lauryl sulfate, dodecyl sulfate, cholesteryl sulfate, and a combination thereof.

13. The sustained-release lipid pre-concentrate of claim 8, wherein the anionic anchoring agent with the sulfonate in the polar head is selected from the group consisting of benzene sulfonate, dodecyl benzene sulfonate, and a combination thereof.

14. The sustained-release lipid pre-concentrate of claim 1, wherein a weight ratio of a) to b) ranges from 10:1 to 1:10.

15. The sustained-release lipid pre-concentrate of claim 1, wherein a weight ratio of a) + b) to c) ranges from 1000:1 to 1:1.

16. The sustained-release lipid pre-concentrate of claim 1, wherein a weight ratio of a) + b) + c) to d) ranges from 5000:1 to 5:1.

17. A pharmaceutical composition, comprising:

the sustained-release lipid pre-concentrate of any one of claims 1 to 16; and

e) at least one cationic pharmacologically active substance,

wherein the anionic anchoring agent of the sustained-release pre-concentrate enhances the sustained release of the cationic pharmacologically active substance by forming an ionic bond with the cationic pharmacologically active substance.

18. The pharmaceutical composition of claim 17, wherein the cationic pharmacologically active substance is selected from the group consisting of pharmacologically active substance having at least one structure of a primary amine, a secondary amine, a tertiary amine, an aromatic amine, a sulfonium, an iodonium, an ammonium, a phosphonium, a pyridinium, a thiazolinium, an imidazolinium, a sulfoxonium, an isothiouronium, an azetidinium or a diazonium, a pharmaceutically acceptable salt thereof, and a combination thereof.

19. The pharmaceutical composition of claim 17, wherein the cationic pharmacologically active substance is selected from the group consisting of leuprolide, triptorelin, goserelin, nafarelin, buserelin, histrelin, deslorelin, meterelin, gonadrelin, entecavir, anastrozole, rivastigmin, acapodene, abiraterone, tibolone, fentanyl, tacrolimus, methotrexate, tamsulosin, dutasteride, finasteride, solifenacin, tadalafil, donepezil,

olanzapine, risperidone, aripiprazole, naltrexone, varenicline, ropinirole, latanoprost, olopatadine, progesterone, ketotifen, montelukast, human growth hormone, tramadol, diazepam, diclofenac, pilocarpine, levocabastine, timolol, betaxolol, carteolol, levobunolol, epinephrine, dipivefrine, clonidine, apraclonidine, indomethacin, acyclovir, testosterone, statin, nifedipine, voriconazole, clotrimazole, ketoconazole, fulvestrant, fibrate, octreotide, estradiol, cortisone, progesterone, amphotericin B, chlorhexidine, corticosteroid, cyclosporine A, desmopressin, somatostatin, calcitonin, oxytocin, vasopressin, follitropin-alpha or beta, thyrotropin alpha, secretin, bradykinin, hypotensive tissue hormone, insulin or insulin derivatives, interferon, tuftsin, magainin, indolicidin, protegrin, polymyxin, gramicidin, vapreotide, exenatide, liraglutide, CJC-1131, AVE010, LY548806, TH-0318, BIM 51077, degarelix, glucagon, defensin, histatin, a pharmaceutically acceptable salt thereof, and a combination thereof.

20. The pharmaceutical composition of claim 17, wherein the cationic pharmacologically active substance is selected from the group consisting of leuprolide, triptorelin, goserelin, nafarelin, buserelin, histrelin, deslorelin, meterelin, gonadrelin, a pharmaceutically acceptable salt thereof, and a combination thereof.

21. The pharmaceutical composition of claim 17, wherein a

weight ratio of a) + b) + c) + d) to e) ranges from 10,000:1 to 2:1.

22. The pharmaceutical composition of claim 17, being formulated into a dosage form selected from among an injection, a ointment, a gel, a lotion, a capsule, a tablet, a solution, a suspension, a spray, an inhalant, an eye drop, an adhesive, and a plaster and pressure sensitive adhesive.

23. The pharmaceutical composition of claim 22, wherein the dosage form is an injection.