



(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/KR2013/012269

(22) International Filing Date:

27 December 2013 (27.12.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10-2012-0157583

28 December 2012 (28.12.2012)

KR

(71) Applicant: CHONG KUN DANG PHARMACEUTICAL CORP. [KR/KR]; 8, Chungjeong-ro, Seodaemun-gu, Seoul 120-756 (KR).

(72) Inventors: YOON, Sang Phil; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KO, Ki Seong; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). YU, Ha Na; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). BAIK, Hye Jung; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si,

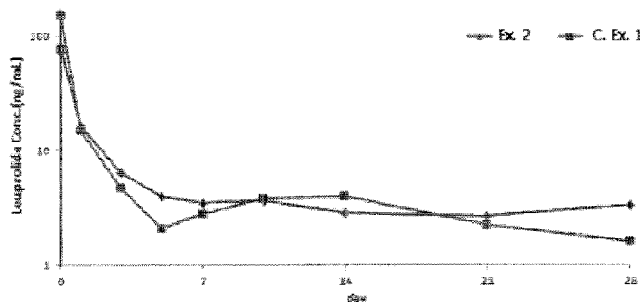
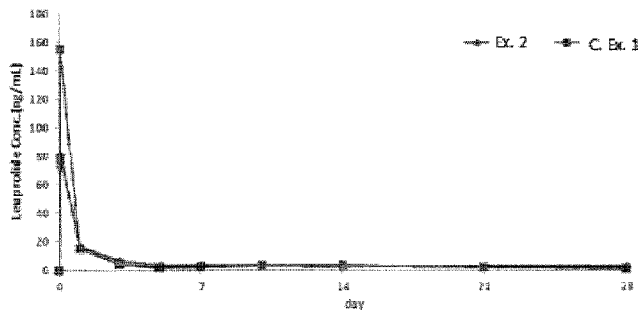
Gyeonggi-do 446-916 (KR). YANG, Won Kyu; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KO, Jin Young; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). PARK, So Hyun; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). JUNG, Sung Bum; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). AN, Sung Won; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KI, Min Hyo; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR).

(74) Agent: AHN, So-Young; Dr. Ahn International Patent Law Office, 10th Fl., 332, Seocho-daero, Seocho-gu, Seoul 137-881 (KR).

(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, 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,

[Continued on next page]

(54) Title: SUSTAINED-RELEASE LIPID PRE-CONCENTRATE OF GnRH ANALOGUES AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME



(57) Abstract: Disclosed is a pharmaceutical composition, comprising: a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH (hydroxyl) groups; b) at least one phospholipid; c) at least one liquid crystal hardener which is free of an ionizable group and has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure in a hydrophobic moiety; and d) at least one GnRH (gonadotropin-releasing hormone) analogue as a pharmacologically active substance, wherein said lipid pre-concentrate exists as a liquid phase in absence of aqueous fluid and forms into a liquid crystal in presence of aqueous fluid. The pharmaceutical composition is configured to enhance the sustained release of the pharmacologically active substance GnRH analogue.

WO 2014/104791 A1

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.

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

(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,

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Description

Title of Invention: SUSTAINED-RELEASE LIPID PRE-CONCENTRATE OF GNRH ANALOGUES AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

Technical Field

- [1] The present invention relates to a sustained-release lipid pre-concentrate comprising a GnRH analogue as a pharmacologically active substance, and a pharmaceutical composition comprising the same.

Background Art

- [2] Sustained release formulations are designed to release a single dose of a pharmacologically active substance at a predetermined rate in order to maintain the effective concentration of the substance in the blood stream for a specific period of time, with minimization of the side effects caused by multiple doses.
- [3] In consideration of the therapeutic mechanism and physical and chemical properties thereof, gonadotropin-releasing hormone (GnRH) derivatives are representative of pharmacologically active substance to be designed as sustained-release formulations.
- [4] Gonadotropin-releasing hormone (GnRH) or luteinizing hormone-releasing hormone (LHRH) is a neuroendocrine peptide which is synthesized and released from neurons in the neurovascular terminal of hypothalamus. Once being released from the hypothalamus, GnRH selectively binds to specific receptors on the membrane of anterior pituitary gonadotroph cells to induce the biosynthesis and release of follicle-stimulating hormone (FSH) and leuteinizing hormone (LH). FSH and LH act to regulate the production of sex steroids from sex glands in males and females. Due to the biological functions of GnRH, its analogues may be useful for the treatment of sex hormone-dependent diseases such as prostate cancer, breast cancer, ovarian cancer, endometriosis, uterine fibroid, polycystic ovary syndrome, hypertrichosis, precocious puberty, gonadotroph pituitary adenomas, sleep apnea syndrome, irritable bowel syndrome, premenstrual syndrome, benign prostatic hyperplasia, and infertility.
- [5] Lupron® Depot is a commercially available, intramuscular or subcutaneous injection for the sustained release of the GnRH analogue leuprolide acetate, with the biodegradable PLGA [poly(lactic-co-glycolic acid)] microparticles delivering as a sustained release matrix. Generally, PLGA microparticles degrade into lactic acid and glycolic acid over a specific period of time in vivo, releasing the pharmacologically active substance loaded there within in a sustained manner (U. S. Patent No. 5,480,656). However, not only are the fabrication processes of PLGA microparticles complicated and difficult, but also pharmacologically active substances are loaded

thereinto with significantly poor efficiency. In addition, because a PLGA microparticles are difficult to filter sterilization, and melt at 40°C or higher, the sterilization thereof cannot be achieved with general processes, but requires highly sterile conditions. An ideal sustained-release profile is obtained using two or more different PLGA microparticles which, however, further complicate the processes of fabrication and mixing (WO 2005/074896), increasing the production cost. In addition, acetic acid impurities and acidic degradation products from PLGA microparticles induce inflammation and reduce cell growth rates (K. Athanasiou, G. G. Niederauer, and C. M. Agrawal, *Biomaterials*, 17, 93 (1996)). For the sustained release, a suspension of 10~100 µm PLGA microparticles in an aqueous solution is injected in a significant amount, but this gives rise to a pain or a tissue damage at the injection site.

- [6] Eligard® was introduced as a sustained-release injection formulation for a GnRH analogue (leuprolide acetate) which compensates the problems with PLGA microparticle-based sustained-release formulations. Eligard® is widely marketed as a subcutaneous injection which is prepared by dissolving PLGA [poly(DL-lactide-co-glycolide)] having a protected carboxyl terminal group and a GnRH analogue (leuprolide acetate) in N-methyl-2-pyrrolidone (NMP). Eligard® exists as a flowable composition which can be prepared by dissolving a biodegradable polymer in a polar aprotic solvent, and is designed as a subcutaneous injection with an improvement in partially drawbacks with solid PLGA microparticle formulations (U. S. Patent No. 6,773,714). This commercial product is very poor in usability because of no supply of a complete prefilled syringes device, and exhibits low drug stability upon the mixture solution. The device provided in the product comprises two syringes which can be connected to each other, and mixing, preparing and injecting tools. A final mixture solution is not obtained until more than about 10 steps are carried out, and only 30 mins is given to an entire process from preparation to injection. In addition, the product must be stored in a refrigerator, and unless stored in a refrigerator, the final mixed solution cannot be used for more than 5 days. Moreover, no improvements are observed in the product with regard to a high initial burst, which is a drawback typical to PLGA microparticle formulations. Rather, the product exhibits higher initial burst concentration, compared to the PLGA microparticle formulation Lupron® Depot (U. S. Patent No. 6,773,714). An initial burst concentration greatly exceeding that at which a drug can function is undesirable in both functionally and toxicologically. Particularly in consideration of the mechanism of the GnRH analogue in which the sex hormone release is temporally increased at an initial stage of administration, and then down-regulated from a certain time point, an excessive initial burst concentration must be avoided.

- [7] As an alternative solution to the problems with PLGA microparticle formulations, the

International Patent Publication No. WO 2005/117830 describes a pre-formulation comprising at least one neutral diacyl lipid and/or at least one tocopherol, at least one phospholipid, and at least one biocompatible, oxygen containing, low viscosity organic solvent. Another alternative is described in the International Patent Publication No. WO 2006/075124 which concerns a pre-formation comprising at least one diacyl glycerol, at least one phosphatidyl choline, at least one oxygen containing organic solution, and at least one GnRH analogue. These pre-formulations allow the sustained release of a pharmacologically active substance in vivo for four weeks, and do not form lactic acid or glycolic acid degradation products from their polymer systems, thus not causing pain or inflammation. However, there is a problem with the formulations in that the use of a diacyl lipid, a component essential for the pre-formulations, as a pharmaceutical excipient is not usable and it has to be proven to be sufficiently safe, and that their obligatory organic solvent incurs a reduction in the activity of some pharmacologically active substances (H. Ljusberg-Wahre, F. S. Nielse, 298, 328-332 (2005); H. Sah, Y. Bahl, Journal of Controlled Release 106, 51-61(2005)).

[8]

[9] Culminating in the present inventors suggested a sustained-release lipid pre-concentrate comprising a) sorbitan unsaturated fatty acid ester; b) a phospholipid; and c) a liquid crystal hardener, and a pharmaceutical composition comprising the pre-concentrate (Korean Patent Application No. 10-2012-0093677). This sustained-release lipid pre-concentrate exhibits in vivo safety and biodegradability at the same or higher levels, compared to conventional pre-concentrates and the pharmaceutical composition is found to allow for the sustained release of the pharmacologically active substance loaded therein.

[10] Moreover, the further research of the present inventors resulted in the finding that when applied to the sustained-release lipid pre-concentrate, a GnRH analogue can be released in a sustained manner at a concentration sufficient to act as a pharmacological active substance in vivo, leading to the present invention.

[11]

[12] A description is given of the prior arts relevant to the present invention, *infra*.

[13] U. S. Pat. No. 7,731,947 describes a composition comprising: a particle formulation comprising an interferon, sucrose, methionine, and a citrate buffer, and a suspending solution comprising a solvent such as benzyl benzoate, wherein the particle formulation is dispersed in the suspending solution, elucidating the application of GnRH analogues thereto. In one Example, it is described that phosphatidylcholine is dissolved together with vitamin E (tocopherol) in an organic solvent and is used to disperse the particle formulation therein. However, this composition is different from the present invention in that the composition is used to disperse solid particles and does not allow

the formation of liquid crystals.

[14] U. S. Pat. No. 7,871,642 describes a method of preparing a dispersion for delivering a pharmacologically active substance comprising hormone formulation, dispersing a homogeneous mixture of a phospholipid, a polyoxyethylene-containing coemulsifier, triglyceride and ethanol in water, wherein the polyoxyethylene-containing surfactant is selected from among polyoxyethylene sorbitan fatty acid esters (polysorbate) and polyethoxylated vitamin E derivatives. polyoxyethylene sorbitan fatty acid esters and polyethoxylated vitamin E derivatives, derived by conjugating the hydrophilic polymer polyoxyethylene to sorbitan fatty acid ester and vitamin E, respectively, are quite different in structure from sorbitan fatty acid ester and vitamin E. They are usually used as hydrophilic surfactants utilizing the property of polyoxyethylene, which is different from the component of the present invention.

[15] U. S. Pat. No. 5,888,533 describes a flowable composition for forming a solid biodegradable implant in situ within a body, comprising: a non-polymeric, water-insoluble, biodegradable material; and a biocompatible, organic solvent that at least partially solubilizes the non-polymeric, water-insoluble, biodegradable material and is miscible or dispersible in water or body fluids, and capable of diffusing-out or leaching from the composition into body fluid upon placement within a body, whereupon the non-polymeric material coagulates or precipitates to form the solid implant. In this composition, sterols, cholesteryl esters, fatty acids, fatty acid glycerides, sucrose fatty acid esters, sorbitan fatty acid esters, fatty alcohols, esters of fatty alcohols with fatty acids, anhydrides of fatty acids, phospholipids, lanolin, lanolin alcohols, and combinations thereof are described as the non-polymeric material, and ethanol is used as the solvent. However, differences from the present invention reside in that this composition cannot form liquid crystals and is designed to form solid implants by simple coagulation or precipitation of water-insoluble materials and that a lot of the organic solvent is necessarily used.

[16]

Disclosure of Invention

Technical Problem

[17] It is therefore an object of the present invention to provide a pharmaceutical composition based on a sorbitan unsaturated ester having a polar head with at least two -OH(hydroxyl) groups that has significantly high safety and biodegradability and exists in a liquid state advantageous for injection applications while forming into a liquid crystal upon exposure to aqueous fluid, thus enhancing the sustained release of a GnRH analogue in vivo.

[18] It is another object of the present invention to provide a pharmaceutical composition

which can be injected without producing pain, inflammations and initial burst concentrate, problems which are reported in conventional formulations.

[19]

Solution to Problem

[20] In accordance with an aspect thereof, the present invention provides a pharmaceutical composition, comprising a) at least one sorbitan unsaturated fatty acid ester; b) at least one phospholipid; c) at least one liquid crystal hardener; and d) at least one GnRH analogue, as a pharmacologically active substance, wherein the composition exists as a liquid phase in the absence of aqueous fluid and forms into a liquid crystal in the presence of aqueous fluid.

[21] Below, a detailed description will be given of each component.

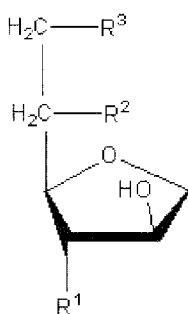
[22]

a) Sorbitan unsaturated fatty acid ester

[24] For use as a liquid crystal former in the present invention, the sorbitan unsaturated fatty acid ester preferably has two or more -OH(hydroxyl) groups in the polar head. This sorbitan unsaturated fatty acid ester is represented by the following Chemical Formula 1. The compound of Chemical Formula 1 is sorbitan monoester where $R^1=R^2=OH$, $R^3=R$, and sorbitan diester where $R^1=OH$, $R^2=R^3=R$, R being an alkyl ester of 4 to 30 carbon atoms with at least one unsaturated bond.

[25] [Chemical Formula 1]

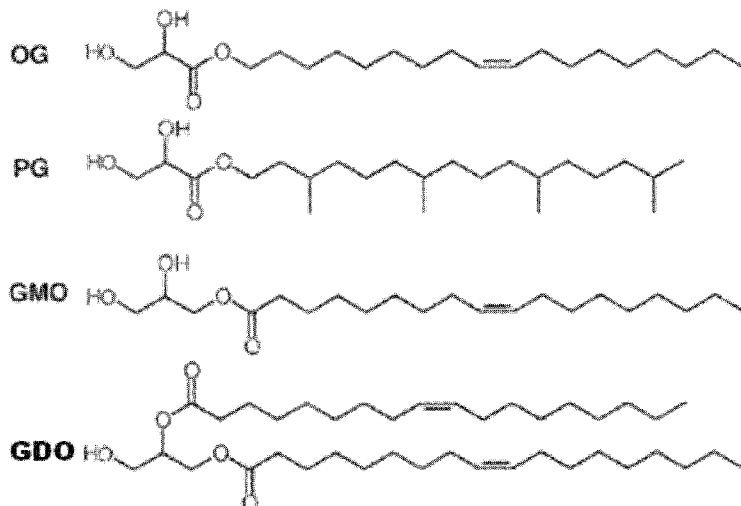
[26]



[27] The sorbitan fatty acid ester, which accounts for the formation of a liquid crystal in the present invention, is different from conventional counterparts such as oleyl glycerate (OG), phytanyl glycerate (PG), and glycerine monooleate (GMO), glycerine dioleate (GDO) of the following Chemical Formula 2. That is, the conventional molecules responsible for liquid crystalline phases share the common structure consisting of a polar head derived from glycerine or glyceric acid and a non-polar tail derived from a lipid alcohol or fatty acid.

[28] [Chemical Formula 2]

[29]



[30] However, the conventional molecules responsible for liquid crystalline phases are somewhat difficult to apply to the development of medications because of the following disadvantages. Oleyl glycerate (OG) and phytanyl glycerate (PG), although capable of readily forming into liquid crystals, are rarely used as pharmaceutical excipients for human medicine because of their relatively high toxicity. On the other hand, glycerine monooleate (GMO) is useful as a pharmaceutically acceptable excipient, but has weak crystallinity to form liquid crystals necessary for sustained release medications.

[31] Glycerol dioleate (GDO), which is used in International Patent Publication No. WO 2005/117830 as described supra, is a diacyl lipid with glycerin functioning as a polar head. This molecule is not generally used as a pharmaceutical excipient because its safety has not yet been proven.

[32] Following intensive and thorough research, the present inventors found that sorbitan unsaturated fatty acid esters have advantages over conventionally used liquid crystalline molecules, glycerine or glyceric acid derivatives in that they form liquid crystals very effectively for the sustained release of pharmacologically active substance, with superiority in safety and biodegradability and are applicable to the development of medical products overcoming the problems encountered in the prior art. For use in compositions for medicaments, materials must be guaranteed to be safe and biodegradable. Further, biodegradability is a very important factor for the material which is in charge of sustained release in the body. If the sustained release injection using PLGA is designed to release a pharmacologically active substance for one week, it is ideal that the PLGA is degraded in vivo one week after injection. In fact, however, PLGA remains intact for one to several months even after the function of sustained release is finished. Therefore, the sorbitan unsaturated fatty acid ester of the present invention, which has excellent sustained release property, safety and biodegradability,

is applicable for a novel liquid crystal-inducing material with great value in pharmaceutical industry.

- [33] In detail, the sorbitan unsaturated fatty acid ester of the present invention may be selected from sorbitan monoester, sorbitan sesquiester, sorbitan diester and a combination thereof, which can be derived from fatty acids obtainable from whale oils and fish oils as well as vegetable oils (e.g., coconut oil, castor oil, olive oil, peanut oil, rapeseed oil, corn oil, sesame oil, cotton seed oil, soybean oil, sunflower seed oil, safflower oil, linseed oil, etc.), and animal fats and oils (e.g., milk fat, lard, and beef tallow).
- [34] Sorbitan monoester is a compound in which one fatty acid group is attached to sorbitan via an ester bond, and may be selected from among sorbitan monooleate, sorbitan monolinoleate, sorbitan monopalmitoleate, sorbitan monomyristoleate, and a combination thereof.
- [35] Sorbitan sesquiester is a compound in which 1.5 fatty acid groups, on average, are attached to sorbitan via an ester bond, and may be selected from among sorbitan sesquioleate, sorbitan sesquilinoleate, sorbitan sesquipalmitoleate, sorbitan sesquimyristoleate, and a combination thereof.
- [36] Sorbitan diester is a compound in which two fatty acid groups are attached to sorbitan via an ester bond, and may be selected from among sorbitan dioleate, sorbitan dilinoleate, sorbitan dipalmitoleate, sorbitan dimyristoleate, and a combination thereof.
- [37] For use in the present invention, sorbitan unsaturated fatty acid ester is preferably selected from sorbitan monooleate, sorbitan monolinoleate, sorbitan monopalmitoleate, sorbitan monomyristoleate, sorbitan sesquioleate, and a combination thereof.
- [38]
- [39] **b) Phospholipid**
- [40] Phospholipids are essential for the construction of lamellar structures, such as liposomes, in conventional techniques, but cannot form a non-lamellar phase structure, such as a liquid crystal, by themselves. However, phospholipids can participate in the liquid crystal former-driven formation of non-lamellar phase structures, serving to stabilize the resulting liquid crystals.
- [41] The phospholipid useful in the present invention is derived from plants or animals, and contains a saturated or unsaturated alkyl ester group of 4 to 30 carbon atoms with a polar head. The phospholipid may be selected from among phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, phosphatidylinositol, phosphatidic acid, sphingomyelin, and a combination thereof according to the structure of the polar head.
- [42] Phospholipids are found in plants and animals such as soybeans and eggs. In phospholipids, long alkyl ester groups which account for the hydrophobic tails include

saturated fatty acid chains such as mono- and dipalmitoyl, mono- and dimyristoyl, mono- and dilauryl, and mono- and distearyl, and unsaturated fatty acid chains such as mono- or dilinoleyl, mono- and dioleyl, mono- and dipalmitoleyl, and mono- and dimyristoleyl. Saturated and unsaturated fatty acid esters may coexist in phospholipids.

[43]

[44] **c) Liquid crystal hardener**

[45] The liquid crystal hardener of the present invention cannot form a non-lamellar structure, unlike the liquid crystal former, nor a lamellar structure such as liposome) unlike phospholipids, by itself. However, the liquid crystal hardener contributes to the liquid crystal former-driven formation of non-lamellar phase structures by increasing the curvature of the non-lamellar structures to enhance the ordered co-existence of oil and water. In the interests of this function, the liquid crystal hardener is advantageously required to have a highly limited polar moiety and a bulky non-polar moiety inside its molecular structure.

[46] In practice, however, biocompatible molecules which are injectable into the body can be selected as the liquid crystal hardener of the present invention only via direct and repeated experiments. As a result, liquid crystal hardeners suitable for the composition of the present invention have molecular structures which are different from one another and thus cannot be elucidated as having only one molecular structure. The common structural feature deduced by observation of all of the liquid crystal hardeners identified is that they are free of ionizable groups, such as carboxyl and amine groups, and have hydrophobic moieties comprising a bulky triacyl group with 15 to 40 carbon atoms or carbon ring structure. Preferred examples of the liquid crystal hardener of the present invention may be free of ionizable groups, such as carboxyl and amine groups, and have at most one hydroxyl and ester group as a weak polar head, with hydrophobic moieties including a bulky triacyl group with 20 to 40 carbon atoms or carbon ring structure. Examples of the liquid crystal hardener of the present invention may include, but are not limited to, triglyceride, retinyl palmitate, tocopherol acetate, cholesterol, benzyl benzoate, ubiquinone, and a combination thereof. Preferably, the liquid crystal hardener may be selected from among tocopherol acetate, cholesterol, and a combination thereof.

[47]

[48] **d) GnRH Analogues**

[49] GnRH analogues are structurally similar to GnRH, but work in different ways in vivo. On the whole, after pulsatile secretion, GnRH performs a biological function to induce the production of sex steroids whereas GnRH analogues are used to potentially inhibit the production of sex steroids for a certain period of time in the body.

[50] According to their acting mechanisms, GnRH analogues may be classified into

agonists and antagonists. When administered at a therapeutic dose to the body, a GnRH agonist initially binds to a GnRH receptor of the pituitary gland to stimulate the biosynthesis and secretion of follicle stimulating hormone (FSH) and leuteinizing hormone (LH). However, continuation of the administration with the GnRH agonist results in the depletion of the gonadotropin and inhibition of the biosynthesis and secretion of FSH and LH while down-regulating the GnRH receptor. Based on the biological functions of GnRH, GnRH analogues may be applied to the treatment of sex hormone-dependent diseases such as prostate cancer, breast cancer, ovarian cancer, endometriosis, uterine fibroid, polycystic ovary syndrome, hypertrichosis, precocious puberty, gonadotroph pituitary adenomas, sleep apnea syndrome, irritable bowel syndrome, premenstrual syndrome, benign prostatic hyperplasia, and infertility, and may be used as a contraceptive.

[51] The GnRH agonist as a pharmacologically active substance of the present invention may be selected from among leuprolide, goserelin, triptorelin, nafarelin, buserelin, histrelin, deslorelin, meterelin, gonadorelin, and a pharmaceutically acceptable salt thereof. Preferably, the pharmacologically active substance may be selected from among leuprolide, goserelin and a pharmaceutically acceptable salt thereof.

[52] On the other hand, a GnRH antagonist competes with GnRH for a GnRH receptor of the pituitary gland to block the binding of GnRH to its receptor, thereby suppressing the biosynthesis and secretion of FSH and LH. Examples of the GnRH antagonist as a pharmacologically active substance of the present invention include degarelix, abarelix, ganirelix, cetorelix, and a pharmaceutically acceptable salt thereof. Preferably, the pharmacologically active substance may be selected from among leuprolide, goserelin and a pharmaceutically acceptable salt thereof.

[53]

[54] In the pharmaceutical composition of the present invention, the weight ratio between components of a) and b) suitable for the formation of liquid crystals is in a range of from 10:1 to 1:10, and preferably in a range of 5:1 to 1:5. The weight ratio of a)+b) to c) falls within the range of from 100:1 to 1:1, and preferably within the range of from 50:1 to 2:1. Given these weight ranges, the components efficiently guarantee the sustained release of liquid crystals and the sustained release behaviors can be controlled by regulating the ratio. The suitable weight ratio of a)+b)+c) to d) for providing the sustained release of the GnRH analogue ranges from 10,000:1 to 1:1, and preferably from 1,000:1 to 1:1.

[55] Preferably, the pharmaceutical composition of the present invention comprises a) in an amount of 9~90 weight %; b) in an amount of 9~90 weight %; c) in an amount of 0.1~50 weight %; and d) in an amount of 0.01~50 weight %.

[56] In another embodiment where the pharmacologically active substance is leuprolide,

the pharmaceutical composition comprises a) in an amount of 9~64 weight %; b) in an amount of 18~76 weight %; c) in an amount of 1~36 weight %; and d) leuprolide, or a pharmaceutically acceptable salt thereof in an amount of 0.1~50 weight % but are not limited thereto.

[57] In another embodiment where the pharmacologically active substance is goserelin, the pharmaceutical composition comprises a) in an amount of 9~64 weight %; b) in an amount of 18~76 weight %; c) in an amount of 1~36 weight %; and d) goserelin or a pharmaceutically acceptable salt thereof in an amount of 0.1~50 weight % but are not limited thereto.

[58] In a further embodiment where the pharmacologically active substance is degarelix, the pharmaceutical composition comprises a) in an amount of 9~64 weight %; b) in an amount of 18~76 weight %; c) in an amount of 1~36 weight%; and d) degarelix or a pharmaceutically acceptable salt thereof in an amount of 2~50 weight % but are not limited thereto.

[59] Given the content ranges of components a) to d), the pharmaceutical compositions of the present invention exhibit excellent sustained release behavior.

[60] As used herein, the term "aqueous fluid" is intended to include water and body fluid such as a mucosal solution, a tear, a sweat, a saliva, a gastrointestinal fluid, an extravascular fluid, an extracellular fluid, an interstitial fluid, and a blood plasma. When brought into body surfaces, regions or cavities (e.g. inside the body) whose external environments are formed for by aqueous fluids, the pharmaceutical composition of the present invention undergoes transition from a liquid phase to a liquid crystalline phase with a semi-solid appearance. That is, the pharmaceutical composition of the present invention exists as a liquid state before application to the human body and shifts into a liquid crystalline phase with sustained release behavior within the body.

[61] The liquid crystals formed by the pharmaceutical composition of the present invention have a non-lamellar phase structure in which oil and water are in an ordered mixture and arrangement without distinction between inner and out phases. The ordered arrangement of oil and water renders the non-lamellar phase structure of a mesophase, which is a state of matter intermediate between liquid and solid.

[62] The pharmaceutical composition of the present invention is different from conventional compositions that are lamellar structures, such as micelles, emulsions, microemulsions, liposomes, and lipid bilayers, which have been widely used in designing pharmaceutical formulations. Such lamellar structures are in oil in water (o/w) or water in oil (w/o) type in which there have an arrangement with inner and out phases.

[63] The term "liquid crystallization," as used herein, refers to the formation of liquid crystals having a non-lamellar phase structure from the pre-concentrate upon exposure to aqueous fluid.

- [64] The pharmaceutical composition of the present invention may be prepared at room temperature from a) at least one liquid crystal former, b) at least one phospholipid, c) at least one liquid crystal hardener, and d) at least one GnRH analogue, and if necessary, by heating or using a homogenizer. The homogenizer may be a high-pressure homogenizer, an ultrasonic homogenizer, a bead mill homogenizer, and etc.
- [65] As described above, the sustained-release lipid pre-concentrate of the present invention may be a pharmaceutical composition which exists in a liquid phase in the absence of aqueous fluid and forms into liquid crystals in the presence of aqueous fluid. As it turns to a pharmaceutical composition which can be applied to the body using a method selected from among injection, coating, dripping, padding, oral administration, and spraying, the pre-concentrate of the present invention may be preferably formulated into various dosage forms including injections, ointments, gels, lotions, capsules, tablets, solutions, suspensions, sprays, inhalants, eye drops, adhesives, plaster and pressure sensitive adhesives.
- [66] Particularly, when an injection route is taken, the pharmaceutical composition of the present invention may be administered by subcutaneous or intramuscular injection or other injection routes depending on the properties of the pharmacologically active substance.
- [67] The pharmaceutical composition of the present invention may be preferably in the formulation form selected from among injections, ointments, gels, lotions, capsules, tablets, solutions, suspensions, sprays, inhalants, eye drops, adhesives, plaster and pressure sensitive adhesives, and more preferably into injections.
- [68] The pharmaceutical composition of the present invention may be prepared by adding a pharmacologically active substance to the pre-concentrate of the present invention. As needed, heat or a homogenizer may be used in the preparation of the pharmaceutical composition of the present invention, but this is not a limiting factor to the present invention.
- [69] The dose of the pharmaceutical composition of the present invention adheres to the well-known dose of the pharmacologically active substance employed, and may vary depending on various factors including the patient's condition, age and sex. It may be administered orally or parenterally depending on the properties of the pharmacologically active substance.
- [70] In accordance with a further aspect thereof, the present invention contemplates a method of maintaining pharmaceutical efficacy through the sustained release of a pharmacologically active substance by administering the pharmaceutical composition of the present invention to a mammal including a human, and the use of the pharmaceutical composition for the sustained release of a pharmacologically active substance.

Advantageous Effects of Invention

[71] As described hitherto, the pharmaceutical composition of the present invention, based on a sorbitan unsaturated fatty acid ester, is highly safe and exists in a liquid phase in the absence of aqueous fluid but rapidly changes into liquid crystals upon exposure to aqueous fluid within the body. Therefore, the pharmaceutical composition can be easily administered, exhibits excellent sustained release of a GnRH analogue without side effects such as pain and inflammation, compared to conventional sustained release formulations in solid particle phases.

[72]

Brief Description of Drawings

[73] FIG. 1 illustrates phase change behaviors of compositions of Examples 2, 6, 9 and 12 upon exposure to aqueous fluid.

[74] FIG. 2 shows the liquid crystalline structures of the compositions of Examples 2 and 6, formed in aqueous fluid.

[75] FIG. 3 shows the in vivo drug release behaviors of the compositions of Example 2 and Comparative Example 1.

[76] FIG. 4 shows the in vivo drug release behaviors of the compositions of Example 6 and Comparative Example 2.

[77]

Mode for the Invention

[78] The following non-limiting Examples serve to illustrate selected embodiments of the invention. It will be appreciated that variations in proportions and alternatives in elements of the components shown will be apparent to those skilled in the art and are within the scope of embodiments of the present invention.

[79] The additives and excipients used in the present invention satisfied the requirements of the Pharmacopoeia and were purchased from Aldrich, Lipoid, Croda, and Seppic.

[80]

[EXAMPLES 1 TO 12] Preparation of Pharmaceutucial Compositions

[82] Sorbitan unsaturated fatty acid esters, phospholipids, liquid crystal hardeners, and pharmacologically active substances were added, at the weight ratios given in Table 1, below.

[83] In Examples 1 to 12, the substances were homogeneously mixed in a water bath maintained at 20~75°C using a homogenizer (PowerGen model 125. Fisher) for 0.5~3 hrs at 1000~3000 rpm. The resulting lipid solutions were left at room temperature to come to thermal equilibrium at 25°C, followed by adding each of the pharmacologically active substances leuprolide acetate, goserelin acetate, and degarelix acetate thereto. Then, the substances were homogenized using a homogenizer for about 5~30

mins at 1,000~3,000 rpm to prepare pharmaceutical compositions in a liquid phase.

[84] [TABLE 1]

[85]

(Unit:mg)	Example											
	1	2	3	4	5	6	7	8	9	10	11	12
Leuprolide acetate	3.75	3.75	3.75	3.75	11.25	11.25	22.5	22.5				
Goserelin acetate									3.78	3.78		
Degarelix acetate											80	80
Sorbitan monooleate		32		35		75		150	36		51.0	25
Sorbitan sesquioleate	43.4		45.8		68		120			35.0		
Phosphatidyl choline		40		45	95	101.3	156	202.6	40	50		35
Phosphatidyl ethanolamine	36.6		40.7				10				38.2	
Tocopherol acetate	6	9		15	45	30	65	60	15	10.0	5.8	12
Cholesterol	10	4	13.5		15	11.3	22	22.6	4			4
Ubiquinone	4									5		
DMSO		5				15		5	5			
Ethanol		10		5		28.1		30				10
Form in aqueous phase	Liquid Crystal											

[86]

[87] **[COMPARATIVE EXAMPLES 1 AND 2]**

[88] For the formulation of Comparative Example 1, Leuplin DPS(CJ) containing leuprolide acetate as a pharmacologically active substance was used in an amount of 3.75 mg.

[89] As the formulation of Comparative Example 2, 11.25 mg of Leuplin DPS(CJ) containing the pharmacologically active substance leuprolide acetate was used.

[90]

[91] **[EXPERIMENTAL EXAMPLE 1] Contents of Pharmacologically Active Substances in Pharmaceutical Compositions**

[92] To examine whether the pharmaceutical compositions prepared in Examples contained pharmacologically active substances at a therapeutically effective concentration, the contents of leuprolide acetate were quantitated by HPLC, as follows.

[93] Each of the pharmaceutical compositions was dissolved in an amount corresponding to 2.5 mg of leuprolide acetate in a mobile phase (triethylamine buffer : acetonitrile : n-propyl alcohol = 85 : 9 : 6), and centrifuged for 10 min at 1500 rpm, followed by filtering the supernatants of the test sample through a 0.2 μm filter. For comparison, a standard sample with the same concentration as that of the test samples was prepared

from a leuprolide acetate standard. The standard sample and the test samples were loaded in an injection volume of 20 μ L at a flow rate of 1.0~1.5 mL/min to 4.6×100 mm, 3 μ m packing L1 column or like, and quantitatively analyzed at 220 nm using a UV spectrometer. Average contents of leuprolide acetate in the pharmaceutical compositions were obtained from three measurements (see Table 2).

[94] [TABLE 2]

[95]

(Unit: %)	Example							
	1	2	3	4	5	6	7	8
Content	100.3	101.2	99.8	98.9	102.9	99.4	100.5	99.1

[96] As can be seen in Table 2, all of the pharmaceutical compositions prepared in Examples 1 to 8 ideally contained leuprolide acetate in amounts within standard content $(100\% \pm 3\%)$.

[97]

[98] **[EXPERIMENTAL EXAMPLE 2] Formation of Liquid Crystals in Aqueous Fluid**

[99] An examination was made to confirm whether the pharmaceutical compositions prepared in Examples form ideal liquid crystals in aqueous fluid. In this regard, the compositions of Examples 2, 6, 9, and 12 which were in liquid phase were loaded into syringes and then injected to 2 g of PBS (pH 7.4). The results are depicted in FIG. 1.

[100] The pharmaceutical compositions prepared in Examples 1 to 12 existed in liquid phase in the absence of aqueous fluid. When injected into an aqueous fluid (PBS), the pharmaceutical compositions in liquid phase forms into spherical liquid crystals, indicating that the pharmacologically active substance GnRH analogue has no influence on the formation of the pharmaceutical compositions into liquid crystals.

[101]

[102] **[EXPERIMENTAL EXAMPLE 3] Structural Determination of Liquid Crystals in Aqueous Fluid**

[103] The liquid crystals of the pharmaceutical compositions of Examples 2 and 6, formed in aqueous fluid, were observed for structure under a polarization microscope (Motic, BA 300 Pol) (FIG. 2).

[104] A slide glass was very thinly coated with each of the pharmaceutical compositions of Examples 2 and 6, and left for 4 hrs in deionized water in a schale to form liquid crystals. After being covered with a cover glass to prevent the introduction of air, the test sample on slide glass was observed at 200x magnification using a polarization microscope (Motic, BA 300 Pol). As can be seen in FIG. 2, the pharmaceutical compositions of Examples 2 and 6 are formed into liquid crystals with typical hexagonal crystalline structures for excellent sustained release.

[105] When an account is taken of results from Experimental Examples 1 to 3, the pharmaceutical compositions of the present invention can form physiochemically stable, ideal liquid crystals in the presence of aqueous fluid even if they contain pharmacologically active substances which have large molecular weights and relatively high hydrophobicity.

[106]

[107] **[EXPERIMENTAL EXAMPLE 4] In Vivo PK Profile of Pharmaceutical Compositions**

[108] Drug release behaviors from the pharmaceutical compositions of the present invention were examined in vivo in the following test.

[109] Using a disposable syringe, each of the pharmaceutical compositions of Examples 2 and 6 was subcutaneously injected at a leuprolide acetate dose of 12.5 mg/kg (corresponding to a 28-day dose for humans) into the back of 6 SD rats (male), 9 weeks old, with an average body weight of 300 g. For comparison with PK profiles of PLGA microparticle formulations, the pharmaceutical compositions of Comparative Examples 1 and 2 were subcutaneously injected at a leuprolide acetate dose of 12.5 mg/kg (corresponding to a 28-day dose for humans) into the back of 6 SD rats (male), 9 weeks old, with an average body weight of 300 g.

[110] Leuprolide acetate concentrations in plasma samples taken from the SD rats were monitored for 28 days using LC-MS/MS (liquid chromatography-mass spectrometry) to draw PK profiles (pharmacokinetic profiles). The average of leuprolide acetate concentration taken from the 6 SD rats are plotted in graph of each of FIG. 3 and 4, and expressed as calculated logarithm values in the lower graph of each of FIG. 3 and 4 to examine a difference in drug concentration of rat plasma at the late phase.

[111] The PK profiles in SD rats of the pharmaceutical compositions of Comparative Example 1 and Example 2 are shown in FIG. 3. As a control (reference drug) for Example 2, Comparative Example 1 was of 3.75 mg of Leuplin DPS(CJ), which is widely used as a 1-month formulation of leuprolide acetate. Compared to the control (reference drug) of Comparative Example 1, the pharmaceutical composition of Example 2 exhibited ideal pK behavior and excellent sustained release. The pharmaceutical composition of Example 2 had an initial burst concentration of 81 ng/mL, which is about half reduced, compared to 155 ng/mL of Comparative Example 1, thus achieving an exceptional improvement in initial burst concentration, a typical problem with PLGA microparticle formulations. In contrast to the composition of Comparative Example 1 which became unstable in PK behavior from 5 days after administration, the pharmaceutical composition of Example 2 maintained very stable effective plasma concentration of leuprolide acetate.

[112] FIG. 4 shows the PK profiles in SD rats of the pharmaceutical compositions of Com-

parative Example 2 and Example 6. As a control (reference drug) for Example 6, Comparative Example 2 was of 11.25 mg of Leuplin DPS(CJ), which is widely used as a 3-month formulation of leuprolide acetate. Compared to the control (reference drug) of Comparative Example 2, the pharmaceutical composition of Example 6 exhibited ideal pK behavior required for sustained release formulations, and particularly excellent sustained release for a long-term. The composition of Comparative Example 2 showed an initial burst concentration about three times as high as that of Comparative Example 1, which was believed to be attributed to the difference of drug content therebetween. Although the pharmaceutical composition of Example 6 was 3-fold higher in drug content than that of Example 2, no observations were made of the rapid increase in initial burst concentration, unlike the composition of Comparative Example 2. The initial burst concentration was measured to be 114 ng/ml, which is about 4-fold smaller than 484 ng/ml, which was measured at the initial phase in the composition of Comparative Example 2. In addition, the composition of Comparative Example 2 had blood leuprolide acetate levels from 10 days after administration, which was significantly lower level compared to the composition of Comparative Example 1 in the mid- to later phase., drawing an unstable PK profile. On the other hand, the pharmaceutical composition of Example 6 allowed for a blood leuprolide acetate level curve which was similar to that of Example 2 in the mid- to late phase, demonstrating that the pharmaceutical composition of the present invention, even though 3-fold increasing in drug content, maintained excellent long-term sustained release.

Claims

- [Claim 1] A pharmaceutical composition, comprising:
- a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH(hydroxyl) groups;
 - b) at least one phospholipid;
 - c) at least one liquid crystal hardener, which is free of an ionizable group, having a hydrophobic moiety of 15 to 40 carbon atoms with a triacyl group or a carbon ring structure; and
 - d) at least one GnRH(gonadotropin-releasing hormone) analogue as a pharmacologically active substance, wherein said lipid pre-concentrate exists as a liquid phase in absence of aqueous fluid and forms into a liquid crystal in presence of aqueous fluid.
- [Claim 2] The pharmaceutical composition 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.
- [Claim 3] The pharmaceutical composition 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.
- [Claim 4] The pharmaceutical composition of claim 1, wherein the phospholipid contains a saturated or unsaturated alkyl ester group of 4 to 30 carbon atoms and is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, phosphatidylinositol, phosphatidic acid, sphingomyelin and a combination thereof.
- [Claim 5] The pharmaceutical composition of claim 4, wherein the phospholipid is phosphatidylcholine.
- [Claim 6] The pharmaceutical composition 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.
- [Claim 7] The pharmaceutical composition of claim 1, wherein the liquid crystal

- hardener is tocopherol acetate, cholesterol, and a combination thereof.
- [Claim 8] The pharmaceutical composition of claim 1, wherein the GnRH analogue is a GnRH agonist or a GnRH antagonist.
- [Claim 9] The pharmaceutical composition of claim 8, wherein the GnRH agonist is selected from the group consisting of leuprolide, goserelin, triptorelin, nafarelin, buserelin, histrelin, deslorelin, meterelin, gonadorelin, a pharmaceutically acceptable salt thereof, and a combination thereof.
- [Claim 10] The pharmaceutical composition of claim 8, wherein the GnRH antagonist is selected from the group consisting of degarelix, abarelix, ganirelix, cetrorelix, a pharmaceutically acceptable salt thereof, and a combination thereof.
- [Claim 11] The pharmaceutical composition of claim 1, wherein the GnRH analogue is selected from the group consisting of leuprolide, goserelin, triptorelin, degarelix, abarelix, a pharmaceutically acceptable salt thereof, and a combination thereof.
- [Claim 12] The pharmaceutical composition of claim 1, wherein the GnRH analogue is leuprolide or a pharmaceutically acceptable salt thereof.
- [Claim 13] The pharmaceutical composition of claim 1, being designed for preventing or treating a sex hormone-dependent disease, or as a contraceptive.
- [Claim 14] The pharmaceutical composition of claim 13, wherein the sex hormone-dependent disease is selected from the group consisting of prostate cancer, breast cancer, ovarian cancer, endometriosis, uterine fibroid, polycystic ovarian disease, precocious puberty, hypertrichosis, gonadotroph pituitary adenomas, sleep apnea syndrome, irritable bowel syndrome, premenstrual syndrome, benign prostatic hyperplasia, and infertility.
- [Claim 15] The pharmaceutical composition of claim 1, wherein a weight ratio of a) to b) ranges from 10:1 to 1:10.
- [Claim 16] The pharmaceutical composition of claim 1, wherein a weight ratio of a)+b) to c) ranges from 1,000:1 to 1:1.
- [Claim 17] The pharmaceutical composition of claim 1, wherein a weight ratio of a)+b)+c) to d) ranges from 10,000:1 to 1:1.
- [Claim 18] The pharmaceutical composition of claim 1, comprising:
a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH(hydroxyl) groups in an amount of 9~90 weight %;

- b) at least one phospholipid in an amount of 9~90 weight %;
- c) at least one liquid crystal hardener which is free of an ionizable group and has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure in a hydrophobic moiety in an amount of 0.1~50 weight %; and
- d) at least one GnRH (gonadotropin-releasing hormone) analogue in an amount of 0.01~50 weight %.

[Claim 19]

The pharmaceutical composition of claim 1, comprising:

- a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH (hydroxyl) groups in an amount of 9~64 weight %;
- b) at least one phospholipid in an amount of 18~76 weight %;
- c) at least one liquid crystal hardener which is free of an ionizable group and has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure in a hydrophobic moiety in an amount of 1~36 weight %; and
- d) leuprolide or a pharmaceutically acceptable salt thereof in an amount of 0.1~50 weight %.

[Claim 20]

The pharmaceutical composition of claim 1, comprising:

- a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH (hydroxyl) groups in an amount of 9~64 weight %;
- b) at least one phospholipid in an amount of 18~76 weight %;
- c) at least one liquid crystal hardener which is free of an ionizable group and has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure in a hydrophobic moiety in an amount of 1~36 weight %; and
- d) goserelin or a pharmaceutically acceptable salt thereof in an amount of 0.1~50 weight %.

[Claim 21]

The pharmaceutical composition of claim 1, comprising:

- a) at least one sorbitan unsaturated fatty acid ester having a polar head with at least two or more -OH (hydroxyl) groups in an amount of 9~64 weight %;
- b) at least one phospholipid in an amount of 18~76 weight %;
- c) at least one liquid crystal hardener which is free of an ionizable group and has a triacyl group with 15 to 40 carbon atoms or a carbon ring structure in a hydrophobic moiety in an amount of 1~36 weight %; and

d) degarelix or a pharmaceutically acceptable salt thereof in an amount of 2~50 weight %.

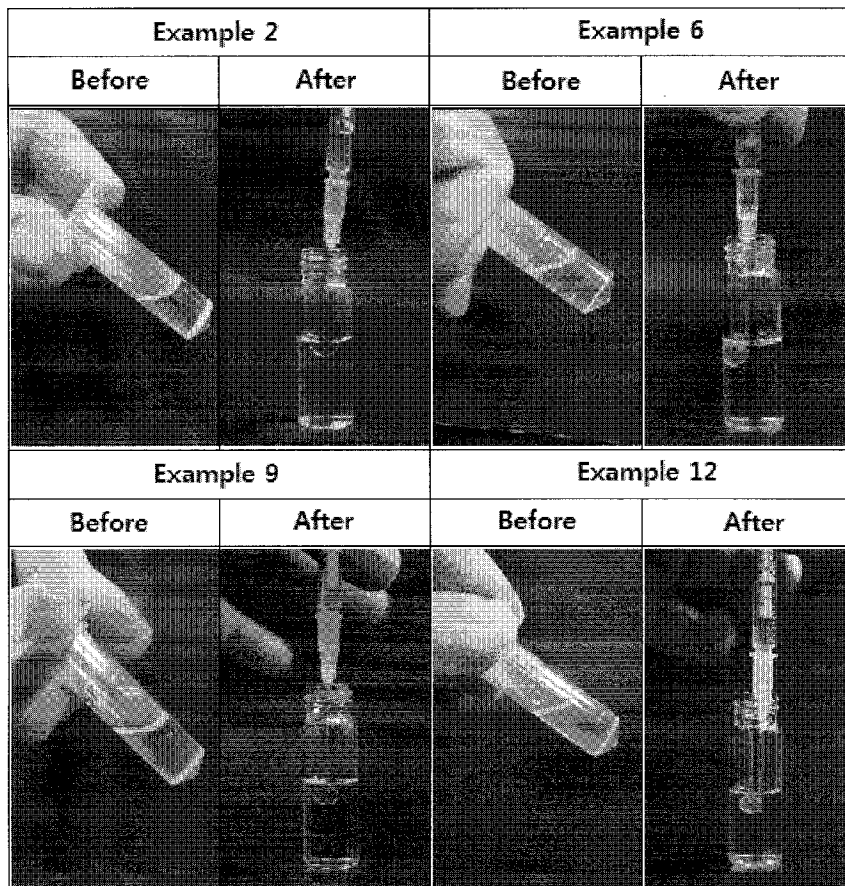
[Claim 22]

The pharmaceutical composition of claim 1, being in a formulation, said formulation being selected from the group consisting of 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.

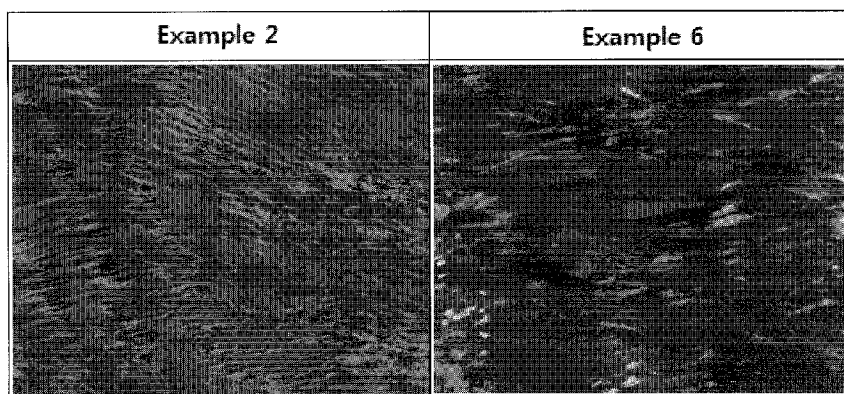
[Claim 23]

The pharmaceutical composition of claim 22, wherein the formulation is an injection.

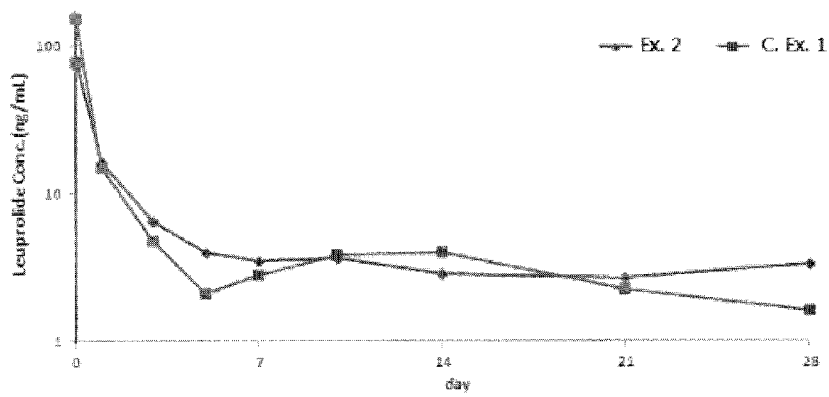
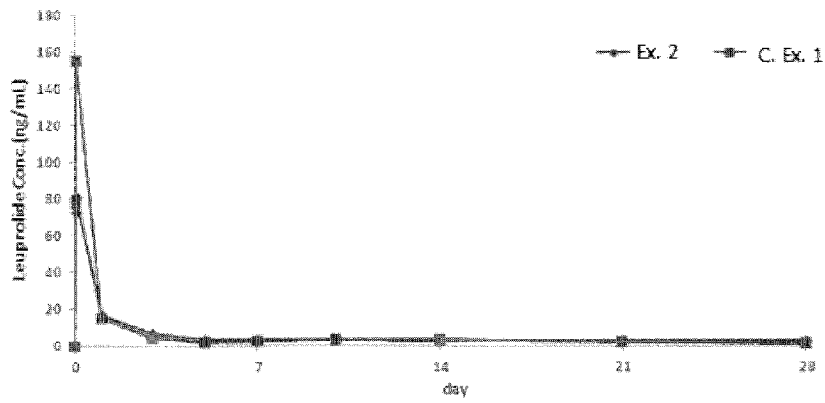
[Fig. 1]



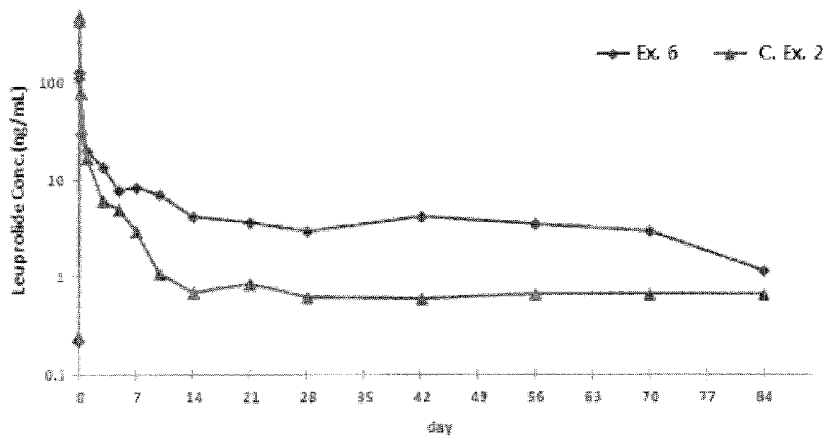
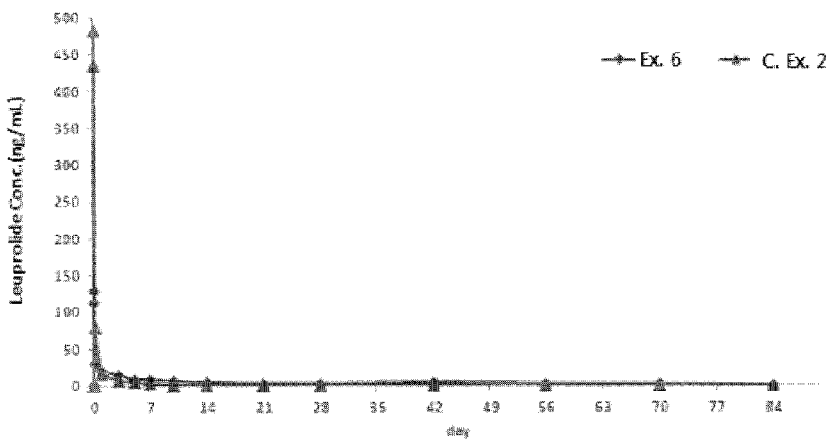
[Fig. 2]



[Fig. 3]



[Fig. 4]



A. CLASSIFICATION OF SUBJECT MATTER**A61K 9/20(2006.01)i, A61K 9/08(2006.01)i, A61K 9/06(2006.01)i, A61K 47/30(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/20; A61P 29/00; A61K 9/14; A61K 37/00; A61K 31/415; A61K 47/24; C09K 19/52; A61K 38/21; A61K 9/08; A61K 9/06; A61K 47/30

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & keywords: liquid crystal, phospholipid, sorbitan, tocopherol, cholesterol, triglyceride, leuprolide, goserelin, GnRH, degarelix

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007-0080323 A1 (JOABSSON, F. et al.) 12 April 2007 See abstract, paragraphs [0017], [0059]-[0062], [0077], [0093], and claims 1, 3, 7, 12, 16, 20.	1-23
X	US 2012-0269772 A1 (THURESSON, K. et al.) 25 October 2012 See abstract, paragraphs [0026], [0044], [0071], and claims 1, 9-12, 16, 18.	1-23
A	US 2008-0274176 A1 (JOHNSSON, M. et al.) 6 November 2008 See abstract, paragraphs [0015], [0033], [0051], [0053], and claims 1, 3-4, 23.	1-23
A	US 5807573 A (LJUSBERG-WAHREN, H. et al.) 15 September 1998 See abstract, column 2, lines 37-43, and claims 1-4, 6.	1-23
A	US 2011-0091420 A1 (LIU, K. et al.) 21 April 2011 See abstract, and claims 1, 4, 10-17, 20.	1-23

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 2014 (28.04.2014)

Date of mailing of the international search report

28 April 2014 (28.04.2014)

Name and mailing address of the ISA/KR

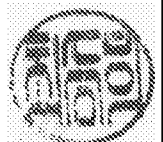
International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City, 302-701,
Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

CHOI, Sung Hee

Telephone No. +82-42-481-8740



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2013/012269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007-0080323 A1	12/04/2007	EP 1682091 A1	26/07/2006
		JP 2007-510705 A	26/04/2007
		WO 2005-046642 A1	26/05/2005
US 2012-0269772 A1	25/10/2012	AT 401054 T	15/08/2008
		AU 2005-249274 A1	15/12/2005
		AU 2005-249274 B2	24/02/2011
		AU 2005-324794 A1	20/07/2006
		AU 2005-324794 B2	13/05/2010
		AU 2005-324794 C1	02/12/2010
		AU 2010-202794 A1	22/07/2010
		AU 2010-202794 B2	27/10/2011
		BR PI0511807 A	15/01/2008
		CA 2569513 A1	15/12/2005
		CA 2569513 C	06/08/2013
		CA 2594710 A1	20/07/2006
		CA 2594710 C	25/01/2011
		CA 2594711 A1	20/07/2006
		CA 2594711 C	06/11/2012
		CA 2594718 A1	20/07/2006
		CA 2594718 C	24/01/2012
		CA 2609810 A1	14/12/2006
		CA 2609810 C	22/05/2012
		CN 101217940 A	09/07/2008
		CN 101217940 B	27/03/2013
		CN 102008728 A	13/04/2011
		DE 602005008247 D1	28/08/2008
		DK 1768650 T3	29/09/2008
		EP 1768650 A1	04/04/2007
		EP 1768650 B1	16/07/2008
		EP 1843746 A1	17/10/2007
		EP 1843746 B1	16/03/2011
		EP 1845942 A1	24/10/2007
		EP 1848403 A1	31/10/2007
		EP 1848403 B1	31/03/2010
		EP 1848403 B8	19/05/2010
		EP 1888031 A1	20/02/2008
		EP 1888031 B1	23/01/2013
		EP 2206495 A1	14/07/2010
		EP 2206495 B1	21/11/2012
ES 2309766 T3	16/12/2008		
IL 179815 A	28/04/2011		
JP 2008-501676 A	24/01/2008		
JP 2008-526932 A	24/07/2008		
JP 2008-526933 A	24/07/2008		
JP 2008-526934 A	24/07/2008		
JP 2008-542437 A	27/11/2008		
JP 2012-214494 A	08/11/2012		
JP 5107725 B2	26/12/2012		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2013/012269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 5127449 B2	23/01/2013
		JP 5144277 B2	13/02/2013
		JP 5171262 B2	27/03/2013
		JP 5198261 B2	15/05/2013
		KR 10-0983746 B1	24/09/2010
		KR 10-1225257 B1	22/01/2013
		KR 10-2007-0046815 A	03/05/2007
		MX PA06014095 A	07/08/2007
		NZ 551990 A	28/01/2011
		RU 2006146009 A	20/07/2008
		RU 2390331 C2	27/05/2010
		SG 173326 A1	29/08/2011
		US 2007-0265190 A1	15/11/2007
		US 2008-0085263 A1	10/04/2008
		US 2008-0124394 A1	29/05/2008
		US 2008-0146490 A1	19/06/2008
		US 2009-0069221 A1	12/03/2009
		US 2009-0155193 A1	18/06/2009
		US 2009-0170782 A1	02/07/2009
		US 2013-0190341 A1	25/07/2013
		US 8097239 B2	17/01/2012
		US 8236292 B2	07/08/2012
		US 8236755 B2	07/08/2012
		US 8545832 B2	01/10/2013
		US 8546326 B2	01/10/2013
		WO 2005-117830 A1	15/12/2005
		WO 2006-075123 A1	20/07/2006
		WO 2006-075124 A1	20/07/2006
		WO 2006-075125 A1	20/07/2006
		WO 2006-131730 A1	14/12/2006
US 2008-0274176 A1	06/11/2008	AU 2005-325510 A1	27/07/2006
		AU 2005-325510 B2	02/07/2009
		CA 2595385 A1	27/07/2006
		CA 2595385 C	25/01/2011
		CN 101123949 A	13/02/2008
		CN 101123949 B	13/06/2012
		EP 1843751 A1	17/10/2007
		JP 2008-528463 A	31/07/2008
		JP 5127466 B2	23/01/2013
		KR 10-1245022 B1	19/03/2013
		KR 10-2007-0103468 A	23/10/2007
		NZ 560568 A	25/02/2011
		WO 2006-077362 A1	27/07/2006
US 05807573 A	15/09/1998	CA 2192190 C	21/09/2004
		EP 0767656 A1	16/04/1997
		EP 0767656 B1	25/07/2001
		JP 10-504532 A	06/05/1998
		JP 3825468 B2	27/09/2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2013/012269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 95-34287 A1	21/12/1995
US 2011-0091420 A1	21/04/2011	CN 102036653 A	27/04/2011
		WO 2009-114959 A1	24/09/2009
		WO 2009-115053 A1	24/09/2009