LOW-OIL PHARMACEUTICAL EMULSION COMPOSITIONS COMPRISING PROGESTOGEN

FIELD OF THE INVENTION

The invention relates to pharmaceutical compositions comprising a progestogen, and to therapeutic or prophylactic treatment of mammals comprising parenteral administration of such a pharmaceutical composition. The compositions according to the invention are particularly suitable for treating a traumatic injury to the central nervous system.

BACKGROUND OF THE INVENTION

Traumatic Brain Injury (TBI) is a non-degenerative, non-congenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairments of cognitive, physical and psychosocial functions with an associated diminished or altered state of consciousness (Brown, A.W., et.al., 2008, Arch. Phys. Med. Rehabil., 89 (Suppl 1), S3-8). TBI is a major cause of death and disability worldwide. It is estimated that more than 1.5 million Americans sustain a TBI each year, and the incidence of TBI in other industrialized countries is comparable to the U.S. (Traumatic Brain Injury: Methods for Clinical and Forensic Neuropsychiatric Assessment, p.2, Granacher, ed., CRC Press 2003). For example, in Europe there are approximately 66,000 deaths annually attributed to TBI (Socin, D.M., et al. (1995). JAMA 273(22), 1778-80). Some patients have a long-term or lifelong need for help to perform activities of daily living as a result of TBI.

Despite the enormity of the problem posed by TBI, there are currently no approved medications proven to be effective in improving mortality or in improving outcomes following TBI. However, two recent clinical trials have demonstrated successful treatment of TBI with the steroid hormone progesterone (Xiao et al, 2008, Crit. Care, 12: R61; Wright et al Ann. Emerg. Med. 2007, 49: 391-402). Both studies showed that progesterone is safe and well tolerated in TBI patients, and that administration of progesterone to TBI patients leads to decreased mortality.

Furthermore, patent applications WO2006/102644, WO2006102596, and WO2008/039898 outline methods for treatment of TBI by parenterally administering progestogen.

The most effective route of administration of progestogens such as progesterone is via parenteral, or intravenous administration. However, the hydrophobic nature of the progesterone molecule, and hence its poor solubility in water, presents formulation limitations. Aqueous solutions do not offer formulations capable of delivering effective therapeutic doses of progesterone to patients. However, progesterone is sufficiently lipophilic to enable therapeutically effective concentrations to be prepared in hydrophobic solvents, such as triglyceride based solvents.

The delivery of hydrophobic drugs via intravenous infusion of oil-in-water emulsions is known in the art. Examples include Taxol® and Abraxane®, which are nanoformulations of the chemotherapy drug paclitaxel designed for intravenous administration, and Diprivan®, which is a lipid emulsion formulation of the anaesthetic propofol marketed by APP pharmaceuticals, IL, USA. Intravenous administration of progesterone with an oil-in-water emulsion has also been previously described (Wright DW et al. supra; Trotter et al, Journal of Clin. Endocrinol. & Metab. (1999) Vol.84, page 4531).

The ProTECT study (Wright et al Ann. Emerg. Med. 2007, 49: 391-402) utilized a 2-component system, wherein progesterone is firstly dissolved in an alcoholic solution (first component), and this alcoholic progesterone solution is subsequently injected into the commercially available lipid emulsion Intralipid® 20% (Fresenius Kabi, Sweden) (second component), and manually mixed (such as by shaking) shortly before intravenous administration of the alcoholic solution/emulsion mixture. There are multiple disadvantages of using this method of preparation.

Firstly, administration of alcoholic solutions to TBI patients is not desirable. Secondly, whilst the presence of alcohol aids solubilisation of the progesterone, low shear manual mixing does not enable all of the progesterone to enter the oil phase. Consequently such emulsions are capable of solubilising only a limited amount of progesterone, and large amounts of lipid must therefore be administered in order to achieve the desired serum-progesterone levels. However, administration of large volumes of emulsion, and/or large amounts of lipid to the patient can have serious consequences, such as induction of hyperlipidemia or oedema.

The patient is, as a result, exposed to an undesirable lipid and/or liquid load and is placed at risk of adverse reactions.

Furthermore, non-dissolved progesterone is susceptible to crystallisation, and subsequently oxidation in the aqueous phase, thus causing not only elevated levels of particulate matter to accumulate in the composition, but also high levels of degradation products of the active ingredient. Indeed, it has been shown that, when an alcoholic solution of progesterone is injected into a commercial lipid emulsion formulation (such as Intralipid® 20%), a fraction of the hormone is found in crystalline form rather than becoming solubilised in the emulsion. This non-solubilized progesterone has been reported to be adsorbed at the surface of the infusion bags and feed ducts. The observation that not all of the progesterone enters the oil phase of these 2 component emulsions leads to uncertainty as to the concentration of progesterone achieved in the final composition, and the bio-availability of the hormone.

Finally, due to stability issues, the progesterone-lipid mixture of 2-component systems must be prepared only hours ahead of administration (i.e. the first component is added to the second component and mixed within hours of use), as the resulting mixture may not be stored at room temperature. It is both time consuming and inconvenient for medical practitioners to prepare such mixtures on demand, and particularly unsatisfactory in the context of TBI therapy, where prompt treatment can be important to patient outcome.

Alternative methods for making hormone-containing emulsions describe the incorporation of hormone directly into the oil during manufacture of the lipid emulsion.

WO96/10991 describes pharmaceutical compositions for transmucosal administration of estradiol in combination with a progestin.

WO 01/28555 describes oil-in-water emulsion systems for the delivery of polyfunctional active ingredients. The emulsions comprise, in addition to an active ingredient, polarity modifiers, capable of modifying the interaction between the polyfunctional active ingredient and the oil phase, by serving as a bridge to reduce the effects of the gap in polarity between the active ingredient and the oil.

US 2007/0071777 describes a method of making a 20% lipid emulsion comprising progesterone, which serves as a stock solution that is used to prepare (by dilution) a 5% lipid emulsion which is suitable for administration.

CN101152186 describes the use of the surfactants Solutol S15 or poloxamer 188 in the preparation of injectable progesterone formulations. Whilst use of these surfactants achieves a high progesterone solubility, intravenous administration of high concentrations of these surfactants is associated with undesirable side-effects including moderate elevation in histamine release, urticaria, and anaphylactic reactions (pruritis, erythema).

Another method of increasing the solubility of progesterone in lipid emulsions known in the art is the use of organic solvents. Progesterone is highly soluble in benzoic acid or its derivatives. For example, JP 60-258110 describes the use of benzyl benzoate to increase progesterone solubility in a lipid emulsion. However, since benzyl alcohols and benzyl benzoate are commonly toxic and are known to elicit allergies, their inclusion in compositions for parenteral administration is considered a serious danger.

Starting from this knowledge, one skilled in the art is faced with several problems intrinsic to emulsions. For example, under most conditions emulsions are thermodynamically unstable, since droplets spontaneously agglomerate, eventually leading to complete phase separation. The tendency for agglomeration and phase separation presents problems of storage and handling, and increases the likelihood that pharmaceutical emulsions initially properly prepared will be in a less optimal, less effective and poorly-characterized state upon ultimate administration to a patient. The presence of hydrophobic active agents in the emulsion, such as progesterone, further exacerbates these problems since the drug itself destabilizes the emulsion. It remains extremely difficult therefore, to formulate heat-sterilizable, and storage-stable emulsions capable of delivering high enough doses of progestogen to be therapeutically useful, whilst also being safe to administer parenterally, especially intravenously.

None of the formulations known to date provide pharmaceutical compositions suitable for parenteral administration, which deliver progestogen in a sufficiently high concentration, whilst exposing the patient to a minimum lipid load and/or volume load. None of the formulations known to date provide pharmaceutical compositions suitable for parenteral administration, which demonstrate sufficient physical and/or chemical stability to enable heat-sterilization and long term storage of the emulsions.

There remains a need for formulations of progestogen which are sufficiently chemically and physically stable to enable them to be sterilized by autoclaving and stored for prolonged time periods, preferably at room temperature, prior to use. Moreover, there remains a need for low-oil formulations which deliver higher doses of progestogen per lipid volume, such that therapeutically effective concentrations of progestogen can be delivered to a subject, whilst exposing the patient to as low as possible a lipid load.

OBJECTS OF THE INVENTION

It is an object of this invention to provide low-oil pharmaceutical emulsion compositions comprising progestogen, which are suitable for parenteral administration.

It is an object of this invention to provide low-oil pharmaceutical emulsion compositions comprising progestogen, having an improved safety profile.

It is a further object of this invention to provide oil-in-water emulsions comprising progestogen which are heat-sterilizable.

It is a further object of this invention to provide oil-in-water emulsions comprising progestogen with improved storage stability, such that they may be provided in a ready-to-use form and stored for prolonged periods prior to use.

It is another object of this invention to provide improved pharmaceutical emulsion compositions, suitable for parenteral administration capable of delivering high doses of progestogen per unit oil administered.

It is a further object of the present invention to provide cost-effective compositions for the safe, effective and convenient parenteral administration of progestogen to subjects. More specifically, it is an object of this invention to provide compositions for parenteral administration, which provide an improved availability of the progestogen contained therein (e.g., good pharmacokinetics and bioavailability, such as may be reflected in serum hormone levels and/or plasma concentrations),

whilst exposing the subjects to which the compositions are administered to a lower lipid and/or lower volume load than compositions of the prior art.

It is a further object of the present invention to provide a method for treating subjects with TBI.

It is an object of the present invention to provide a method of manufacturing oil-in-water emulsions comprising progestogen.

SUMMARY

The present disclosure provides pharmaceutical compositions comprising progestogen, such as progesterone, wherein said compositions are in the form of an emulsion comprising an aqueous phase, an oil, and a surfactant. The disclosed compositions advantageously have a low oil content, are ready-to-use, heat-sterilizable, storage-stable, and safe to administer by injection.

The present disclosure also provides methods for parenteral administration of the disclosed pharmaceutical compositions. Such methods advantageously expose the subject to which they are administered to a lower lipid level than compositions of the prior art. The compositions disclosed herein advantageously enable a higher concentration of progestogen to be delivered per unit oil and/or volume, to a subject in need thereof.

The present disclosure is also directed to methods of treatment of central nervous system conditions, and especially traumatic brain injury, with the disclosed compositions, and to a method of manufacturing the pharmaceutical compositions.

In one aspect, the invention provides a sterile, ready-to-use, pharmaceutical oil-in-water emulsion composition for parenteral administration comprising:

- 0.015 to 0.5% wt./vol., preferably 0.05 to 0.4% wt/vol. progesterone;
- 0.5 to 10% wt./vol. of oil, wherein the oil comprises at least 85% wt./wt. triglyceride;
- 0.0425 to 4.1% wt./vol., preferably 0.064 to 3.4% wt./vol. of phospholipid;
- 80-99.4% wt./vol. aqueous medium;

wherein the composition has an osmolality in the range of 200-1000 mOsm/kg, and wherein the emulsion contains no more than 1.2% wt/wt of polyethylene glycol 15-hydroxystearate.

In another aspect, the invention provides a method of manufacturing a composition as defined herein, said method comprising the steps of:

a. combining water, phospholipid and optionally an osmotic agent to produce an aqueous composition;
b. combining progesterone and oil to produce an oily composition;
c. combining the aqueous composition and the oily composition followed by homogenization to form a homogenous oil-in-water emulsion.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides pharmaceutical compositions comprising progestogen, wherein said compositions are in the form of an emulsion comprising an aqueous phase, an oil phase, and one or more surfactants.

One embodiment of the present invention provides a sterile, ready-to-use, pharmaceutical oil-in-water emulsion composition for parenteral administration comprising:

- 0.015 to 0.5 % wt./vol. of progesterone;
- 0.5 to 10% wt./vol. of oil, wherein the oil comprises at least 85% wt.wt. triglyceride;
- 0.0425 to 4.1% wt./vol., preferably 0.064 to 3.4% wt./vol, of phospholipid;
- 80-99.4% wt./vol. aqueous medium;

wherein the composition has an osmolality in the range of 200-1000 mOsm/kg. This particular embodiment of the invention is referred to herein as the "Progesterone embodiment".

Another embodiment of the present invention provides a sterile, pharmaceutical, oil-in-water emulsion composition for parenteral administration comprising:

- an oil;
- an aqueous phase;
- a progestogen, preferably progesterone;

wherein the progestogen:oil wt./wt. ratio is greater than 1:32, and wherein the composition contains less than 2.5% wt./vol. benzyl benzoate, and preferably contains less than 1.5% wt./wt. polyethylene glycol 15-hydroxystearate. This second embodiment is referred to herein as the "Progestogen/oil embodiment".

DEFINITIONS

The term "oil" as used herein is readily interchangeable with "lipid" and "fat", and refers to lipophilic high-boiling organic compounds that are liquid at body temperatures, (e.g. about 37°C), and are pharmacologically acceptable in injectable formulations. The oils of the present invention encompass both glycerides, partial glycerides, fatty acid residues and non-glycerides (e.g. cholesterol), as well as mixtures thereof. Phospholipids, unless otherwise indicated, are not encompassed by the term "oil" as used herein.

The term "oil-in-water emulsion" as used herein, refers to a colloidal dispersion system in which liquid oil is dispersed in small droplets (the discrete phase) in an aqueous medium (the continuous phase).

As used herein, the singular forms "a", "an" and "the" designate both the singular and the plural, unless expressly stated to designate the singular only.

As used herein, the phrase "therapeutically effective amount" means that drug dosage that provides the specific pharmacological response for which the drug is administered in a subject in need of such treatment. It is emphasized that a therapeutically effective amount or therapeutic level of a drug will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art. For convenience only, exemplary dosages, drug delivery amounts, therapeutically effective amounts and therapeutic levels are provided below with reference to adult human subjects. Those skilled in the art can adjust such amounts in accordance with standard practices as needed to treat a specific subject and/or condition/disease.

The term "phospholipid" as used herein refers an ester of glycerol with one or two fatty acids and one phosphate ion. In addition to glycerol-derived phopholipids, the term "phospholipid" as used herein also encompasses sphingomyelin.

The term "aqueous medium" as used herein refers to a water-containing liquid.

The term "low-oil" as used herein refers to compositions having a total lipid content wt./vol. of less than or equal to 10%.

The term "high-oil" as used herein refers to compositions having a total lipid content wt./vol. of greater than 10%.

Unless indicated otherwise, whenever reference is made herein to "percentage weight per volume", or "% wt./vol." these terms describe the mass of the component in g per 100 mL of the composition in which it is contained.

Unless indicated otherwise, whenever reference is made herein to "percentage weight per weight" or "% wt./wt." these terms denote the mass of a component as a percentage of the mass of the composition in which the component is contained.

Whenever "volume-weighted percentage fat >5 μm", or "$PFAT_5$" is referred to herein, what is meant is volume-weighted percentage of dispersed fat having a diameter of more than 5 μm measured according to the method described in USP, chapter <729>, Method II, using the Accusizer (780 Automatic Particle Sizer).

Whenever "PCS" or (Photon Correlation Spectroscopy) is referred to herein, what is meant is PCS as measured according to the method described in USP, Chapter <729>, Method I, using the Zetasizer 1000 HSA (Malvern Instruments).

Whenever "D[4,3]" (volume-based median diameter) or d(0,5) (volume-based mean diameter) is referred to herein, what is meant is D[4,3] or d(0,5), measured according to the method described in USP <429> (Light diffraction measurement of particle size), using the Mastersizer 2000 with Hydro S dispersion unit (Malvern Instruments).

Whenever "zeta-potential" is referred to herein, what is meant is the electrokinetic potential in colloidal systems as determined experimentally using Zetasizer 1000 HAS (Malvern Instruments).

Whenever the term "free of crystalline solid" is used herein, it is meant that emulsions of the present invention meet the standards for particulate size and count in injection liquids (USP 788, Method 2- Microscopic Particle count test).

The compositions according to the present invention are suitable for parenteral, especially intravenous administration. Accordingly, the use of the emulsions of the present invention for parenteral administration is a second embodiment of the invention. The invention provides methods for treating a traumatic CNS injury, more particularly, a traumatic brain injury (TBI), by administering to a subject said progestogen-comprising emulsion in a therapeutically effective amount. The treatment of other CNS disorders and the relief of their symptoms is also contemplated, as discussed further herein below.

The invention further provides a process for the preparation of oil-in-water progestogen-comprising compositions.

The emulsion compositions according to the present invention advantageously have a low oil content such that less lipid is delivered to the subject per unit volume, such that adverse side effects such as hyperlipidemia may be avoided. The emulsion compositions according to the present invention advantageously may be heat-sterilized by autoclaving at 121°C for 15 min without compromising the physical or chemical integrity of the emulsions. Sterilization by autoclaving is beneficial not only in terms of microbiological safety, but also is financially more cost-effective.

The emulsion compositions according to the present invention are advantageously provided in a sterile, ready-to-use form and have a shelf life of 1 or 2 years at room temperature.

In one embodiment, the emulsion compositions of the present invention advantageously achieve improved progestogen solubility in oil, whilst maintaining, or

improving, the chemical stability and/or physical stability of the emulsions. In other embodiments the emulsion compositions according to the present invention advantageously have a high progestogen-to-oil ratio such that the desired serum progestogen levels may be reached with minimal oil administered.

Furthermore, the emulsion compositions of the present invention benefit from safety advantages over the prior art, in that for example, a) the TBI subject is exposed to less lipid per unit progestogen upon administration, b) the emulsions meet the standards for particle size and count in injection liquids, USP 788, Method 2 and/or comprise a lesser level of progestogen crystals, the emulsion compositions c) have a low $PFAT_5$ value, d) contain lower levels of chemical impurities, e) may be autoclaved using the gold standard method for microbiological safety, f) do not comprise alcohol or potentially toxic organic solvents, and/or g) the compositions may be stored without compromising the physical stability of the emulsion.

Administration of the compositions on the present invention advantageously gives an improved consistency in patient dosing, relative to compositions of the prior art. This is achieved by optimizing the progestogen to oil to phospholipid ratio of the emulsions, such that the progestogen is fully solubilized in the oil phase, and is consequently fully bio-available.

Administration of the pharmaceutical compositions of the present invention enables larger doses of progestogen to be administered, per unit volume and/or per unit oil, relative to emulsions of the prior art, hence a higher serum progestogen level may be achieved, and a lower plasma triglyceride level may be achieved, compared to administration of compositions of the prior art.

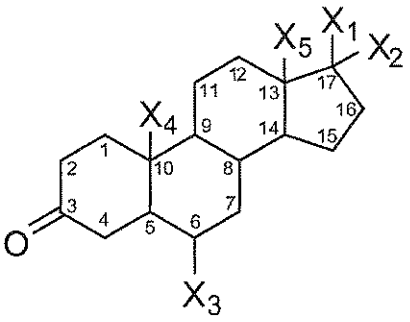
Components of the Composition

Progestogen employed in the "Progestogen/oil embodiment"

The compositions according to the above embodiment of the present invention comprise progestogen as an active pharmaceutical ingredient (API). As used herein, "progestogen" includes both natural progesterone and synthetic progestogens. In general, the progestogens have the general Formula I, wherein X_1 and X_2 are independently selected from $COCH_3$, $OCOC_5H_{11}$, OH, C≡CH, $OCOCH_3$, H, $CH_2C{\equiv}N$; wherein X_3 is selected from H, CH_3, or Cl; wherein X_4 is selected from H, OH, or CH_3; and wherein X_5 is selected from CH_3 or CH_2CH_3. The progestogens may contain ring

structures with one of more double bonds, for example between carbons 3 and 4, 4 and 5, 5 and 6, 6 and 7, 5 and 10, 10 and 9, and/or 15 and 16.

Formula I



Such progestogens include, for example, progesterone and derivatives of progesterone such as 5-alpha-dihydroprogesterone, 6-dehydro-retroprogesterone (dydrogesterone), hydroxyprogesterone caproate, levonorgestrel, norethindrone, norethindrone acetate; norethynodrel, norgestrel, medroxyprogesterone, chlormadinone, and megestrol. The progestogen of the present invention also includes, but is not limited to modifications that produce 17alpha-OH esters of progesterone, as well as, modifications that introduce 6-α-methyl, 6-methyl, 6-ene, and 6-chloro substituents onto progesterone, and/or 19-nor-progesterones. Further, non-limiting examples, of synthetic progestogens include, norethindrone (Micronor®), norgestrel (Ovrette®), levonorgestrel (Norplant®; with ethinyl estradiol; Alesse®, Nordette®), gestodene, medroxyprogesterone acetate (Provera®), promegestone, nomegestrol acetate, lynestrenol and dienogest.

In one embodiment, the progestogen is selected from the group consisting of progesterone, norethynodrel, norethidrone acetate, medroxyprogesterone, medroxyprogesteron 17-acetate, levonorgestrel, dydrogesterone, hydroxyprogesterone caproate, norethidrone, gestodene, nomegestrol acetate, promegestone, dienogest, chlormadinion, megestrol, megestrol acetate, and/or mixtures thereof.

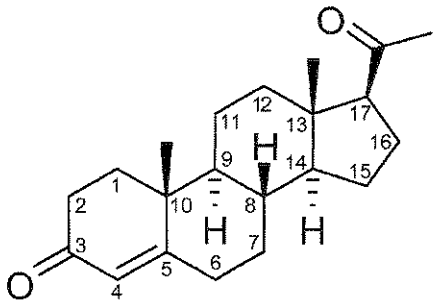
In a preferred embodiment the progestogen is selected from the group consisting of 5-alpha-dihydroprogesterone, medroxyprogesterone, dydrogesterone, and progesterone and/or mixtures thereof.

In a highly preferred embodiment, the progestogen is progesterone.

Progesterone

The term "progesterone" as used herein refers to a member of the progestogen family having the structure of Formula II below:

Formula II



Progesterone is also known as D4-pregnene-3,20-dione; delta-4-pregnene-3,20-dione; or pregn-4-ene-3,20-dione. In an even more preferred embodiment, the progesterone is micronized. Proquina (Mexico) is one supplier of micronized progesterone.

Progestogen (including progesterone)

The progestogen of the present invention may be in the form of a pharmaceutically acceptable salt.

The compositions according to the "progestogen/oil embodiment" suitably comprise an amount of progestogen of at least 0.015 % and not more than 0.5 % wt./vol.

Preferably, the compositions according to both the "Progestogen/oil embodiment" and the "Progesterone embodiment" comprise an amount of progestogen/progesterone of at least 0.03%, more preferably at least 0.05%, even more preferably at least 0.1%, most preferably at least 0.16% weight per total volume (wt./vol.).

The compositions according to the present invention preferably comprise an amount of progestogen/progesterone less than or equal to 0.4%, more preferably less than or equal to 0.3%, even more preferably less than or equal to 0.25% (wt./vol.).

In a particularly preferred embodiment the compositions according to the present invention comprise 0.2% weight per total volume of progesterone, preferably micronized progesterone.

Other pharmaceutically active ingredients

The compositions according to the present invention may comprise one or more further therapeutic ingredients (APIs), such as other neurotrophic and/or neuroprotective agents. Such agents include, for example, compounds that reduce glutamate excitotoxicity and enhance neuronal regeneration. Such agents may be selected from, but are not limited to, the group comprising growth factors. By "growth factor" is meant an extracellular signaling molecule that stimulates a cell to grow or proliferate. In one embodiment the compositions further comprise Vitamin D as a second therapeutic agent, preferably in an amount sufficient to provide a dose of 200 to 1000 IU per day. For example, in certain embodiments the compositions may comprise Vitamin D in a concentration of 0.1 IU/ml to 5 IU/ml, preferably 0.5 IU/ml to 3 IU/ml.

In other embodiments the compositions of the present invention do not contain any further active pharmaceutical ingredients. In a particularly preferred embodiment the compositions of the present invention do not contain estradiol, more preferably they do not comprise estrogen.

Oil phase

The compositions of the present invention are oil-in-water emulsions. The hydrophobic phase (or oil phase) of compositions according to the present invention is or comprises an oil.

Triglycerides are preferred oils. Preferably the hydrophobic/oil phase comprises a triglyceride that has a melting point of less than 30 °C, more preferably of less than 20 °C, and most preferably of less than 10 °C.

The compositions according to the "Progestogen/oil embodiment" suitably contain oil comprising at least 75% wt./wt. triglycerides, more preferably at least 85% wt./wt. triglycerides.

In highly preferred embodiments of both the "Progestogen/oil embodiment" and the "Progesterone embodiment", the hydrophobic phase is an oil, comprising at least 90% wt./wt. triglycerides, most preferably at least 95% wt./wt. triglycerides. In a

preferred embodiment the oil phase comprises "long-chain triglycerides" (LCT) in an amount of at least 45% wt/wt of the total oil, preferably at least 65% wt/wt, more preferably at least 75% wt/wt, most preferably at least 90% wt/wt.

In certain embodiments the preferred oil of the emulsions of the present invention is or comprises a vegetable oil. "Vegetable oil" refers to oil derived from plant seeds or nuts. Vegetable oils are typically "long-chain triglycerides" (LCT), formed when three fatty acids (usually 14 to 22 carbons in length, with unsaturated bonds in varying numbers and locations, depending on the source of the oil) form ester bonds with the three hydroxyl groups on glycerol. In certain embodiments, vegetable oils of highly purified grade (also called "super refined") are used to ensure safety and stability of the oil-in-water emulsions. In certain embodiments hydrogenated vegetable oils, which are produced by controlled hydrogenation of the vegetable oil, may be used in the present invention.

Exemplary vegetable oils include but are not limited to almond oil, babassu oil, black currant seed oil, borage oil, canola oil, caster oil, coconut oil, corn oil, cottonseed oil, olive oil, peanut oil, palm oil, palm kernel oil, rapeseed oil, safflower oil, soybean oil, sunflower oil and sesame oil. Hydrogenated and/or or partially hydrogenated forms of these oils may also be used. Preferred oils are safflower oil, sesame oil, corn oil, olive oil and/or soybean oil. Most preferred oils are safflower oil, and/or soybean oil.

Compositions wherein the oil phase is soy bean oil are most highly preferred. In particularly preferred embodiments the soybean oil may have a palmitic acid content of between 9 and 13%, a stearic acid content of between 2.5% and 5%, an oleic acid content of between 17% and 30%, a linoleic acid content of between 48% and 58%, and a linolenic acid content of between 5% and 11%.

In a preferred embodiment the emulsion compositions comprise no more than 3% wt/wt, more preferably less than 2% wt/wt and most preferably less than 1% wt/wt of structured triglycerides. A "structured triglyceride" as used herein is a triglyceride comprising triglycerides or mixtures of triglycerides having at least one fatty acid group with a carbon chain length of from 6 to 12 carbon atoms and at least one fatty acid group with a carbon chain length of more than 12 carbon units.

In another embodiment the emulsion compositions comprise structured triglycerides in an amount expressed as % wt./wt. of the total oil phase, of no more than

30%, preferably no more than 20%, more preferably no more than 10%, most preferably no more than 5%.

In certain embodiments, the oil of the oil-in-water emulsion compositions described herein may additionally or alternatively comprise medium chain triglycerides. "Medium chain triglycerides" (MCTs) are another class of triglyceride oil that can be either naturally derived or synthetic. MCTs are formed from fatty acids of 6 to 10 carbons in length. MCTs are used extensively in emulsions for injection as a source of calories. Such an oil is commercially available as for example Miglyol 812 (SASOL GmbH Germany), or CRODAMOL GTCC-PN (Croda Inc, New Jersey). Other low-melting medium chain oils may also be used in the present invention. In certain embodiments combinations of vegetable oil and MCT oil are used in the present invention. In preferred embodiments the oil contained in the compositions of the present invention comprises less than or equal to 35% (wt/wt) medium chain triglycerides (MCT), preferably less than or equal to 25% (wt/wt) MCT, more preferably less than or equal to 10% (wt/wt) MCT, most preferably less than or equal to 5% (wt./wt) MCT.

In another embodiment the oil-phase comprises animal fat. "Animal fat" refers to oil derived from an animal source. Animal fat also comprises triglycerides, but the lengths of, and unsaturated bonds in, the three fatty acid chains vary, compared to vegetable oils.

Animal fats from sources that are solid at room temperature can be processed to render them liquid if desired. Other types of animal fats that are inherently liquid at room temperature include marine oils, such as fish oils. Fish oil triglycerides usually have fatty acids having from 12 to 22 carbon atoms. Examplary fish oils include, for example, highly purified fish oil concentrates.

In certain embodiments the oil-phase is a mixture of one or more of an LCT oil and/or an MCT oil and/or an oil of marine origin. Whilst MCTs reportedly enable better solubilisation of active ingredients compared to the less polar LCTs, the presence of predominantly MCTs in emulsions for injection is associated with adverse metabolic effects, and may thus present safety and stability issues. Furthermore, hydrolysis products of MCTs, such as caprylic acid esters, are known to have detrimental neurological side effects. In preferred embodiments, the compositions of the present invention therefore comprise no more than 3%wt/wt MCT, preferably no more than 2%

wt/wt MCT, most preferably no more than 1%wt/wt MCT. In preferred embodiments the emulsions of the present invention do not contain MCT oils.

In one embodiment the emulsion contains no more than 0.9% wt/wt, preferably no more than 0.8% wt/wt, more preferably no more than 0.5% wt/wt of a polarity modifier selected from the group consisting of monoglycerides, diglycerides, acetylated monoglycerides, acetylated diglycerides and/or mixtures thereof. In another embodiment the emulsion contains no more than 0.9% wt/wt, preferably no more than 0.8% wt/wt, more preferably no more than 0.5% wt/wt monoglyceride.

Expressed differently, the emulsion preferably contains not more than 30%, more preferably not more than 20%, even more preferably not more than 10% and most preferably not more than 5% by weight of phospholipid, of a polarity modifier selected from the group consisting of monoglycerides, diglycerides, acetylated monoglycerides, acetylated diglycerides and/or mixtures thereof. The use of a polarity modifier in a significant concentration relative to the phospholipid content of the emulsions is believed to have an adverse effect on the stabilizing properties of the phospholipid.

In another embodiment, the compositions comprise a polarity modifier selected from the group consisting of monoglycerides, diglycerides, acetylated monoglycerides, acetylated diglycerides and/or mixtures thereof, in an amount expressed as % wt./wt. of the total oil phase, of less than 20%, preferably less than 10%, more preferably less than 5%, most preferably less than 2%.

In another embodiment the oil phase comprises less than or equal to 10% wt/wt of the total oil monoglycerides and/or acetylated monoglycerides.

The total oil content (wt./vol.) of the compositions according to the "Progestogen/oil embodiment" of the present invention is at least 0.5% and not more than 10% (wt/vol).

The total oil content of the compositions according to both the "Progesterone embodiment" and the "Progestogen/oil embodiment" preferably is at least 1%, more preferably at least 2%, even more preferably at least 4%, most preferably at least 5% (wt/vol). The total oil component of the emulsion of the present invention is preferably less than or equal to 9% (wt./vol.), even more preferably less than or equal to 8% (wt./vol.), and most preferably less than or equal to 7% (wt./vol.). In a highly preferred embodiment the compositions of the present invention comprise 6% wt./vol. oil, preferably soy bean oil. Preferred soybean oils may have a linoleic acid content of

greater than 48%, and an oleic acid content of greater than 17%. An example of a soybean oil having these properties is refined Soya-bean oil by Fresenius Kabi (Sweden).

In certain embodiments, a substantial proportion of the progestogen is comprised within the oil droplets of the oil-in-water emulsion. In certain embodiments in excess of 80% of the progestogen is dissolved and remains within the oil droplets. In certain embodiments greater than 85%, 90%, 92%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% of the progestogen is dissolved in the oil phase.

Aqueous Medium

The oil-in-water emulsions of the present invention further comprise an aqueous medium. "Aqueous medium" or "aqueous phase" refers to a water-containing liquid. In preferred embodiments the aqueous medium is water and/or an aqueous buffer solution. The compositions according to the "Progestogen/oil embodiment" of the present invention suitably comprise 80-99.4% wt./vol. Preferably, the compositions according to both the "Progestogen/oil embodiment" and the "Progesterone embodiment" comprise 90-97% wt./vol. aqueous medium.

The compositions according to the present invention also optionally comprise 0 to 4 mM of a physiologically compatible buffering agent.

Phospholipid

The compositions of the present invention further comprise one or more emulsifiers/surfactants, including phospholipid. The emulsifiers used in present invention are preferably of natural origin. Naturally occurring emulsifiers include soy lecithin, egg lecithin, sunflower oil lecithin, sphingosine, gangliosides, and phytosphingosine and combinations thereof. Hydrogenated lecithin, i.e. the product of controlled hydrogenation of lecithin, may also be used in the present invention.

The compositions according to the "Progestogen/oil embodiment" of the present invention suitably comprise 0.0425 % to 4.1% wt./vol., preferably 0.064% to 3.4% wt./vol. phospholipid.

Exemplary phospholipids useful in the present invention include, but are not limited to phosphatidyl choline, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid and mixtures thereof. These typically have 4 to 22 carbon atoms, and

more generally from 10 to 18 carbon atoms and varying degrees of saturation. The phospholipid component of the oil-in-water emulsion can be either a single phospholipid or a mixture of several phospholipids. The phospholipids employed may be natural or synthetic, but should be acceptable for parenteral, especially intravenous, administration.

A non-exhaustive list of suitable phospholipids is listed below: phosphatidic acids, including 1,2-Dimyristoyl-sn-glycero-3-phosphatidic acid, sodium salt (DMPA,Na), 1,2-Dipalmitoyl-sn-glycero-3-phosphatidic acid, sodium salt (DPPA,Na),1,2-Distearoyl-sn-glycero-3-phosphatidic acid, sodium salt (DSPA,Na); phosphocholines, including 1,2-Dilauroyl-sn-glycero-3-phosphocholine (DLPC), 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC); phosphoethanolamines, including 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine (DLPE), 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE), 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE); phosphoglycerols, including 1,2-Dilauroyl-sn-glycero-3-phosphoglycerol, sodium salt (DLPG, Na), 1,2-Dimyristoyl-sn-glycero-3-phosphoglycerol, sodium salt (DMPG, Na), 1,2-Dimyristoyl-sn-glycero-3-phospho-sn-1-glycerol, ammonium salt (DMP-sn-1-G,NH4), 1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol, sodium salt (DPPG,Na), 1,2-Distearoyl-sn-glycero-3-phosphoglycerol, sodium salt (DSPG,Na), 1,2-Distearoyl-sn-glycero-3-phospho-sn-1-glycerol, sodium salt (DSP-sn-1G,Na); phosphoserines, including 1,2-Dipalmitoyl-sn-glycero-3-phospho-L-serine, sodium salt (DPPS,Na); mixed chain phospholipids, including 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol, sodium salt (POPG,Na), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol, ammonium salt (POPG,NH4); lysophospholipids, including 1-Palmitoyl-2-lyso-sn-glycero-3-phosphocholine (P-lyso-PC), 1-Stearoyl-2-lyso-sn-glycero-3-phosphocholine (S-lyso-PC); pegylated phospholipids, including N-(Carbonyl-methoxypolyethyleneglycol 2000)-MPEG-2000-DPPE, sodium salt, N-(Carbonyl-methoxypolyethyleneglycol 5000)-MPEG-5000-DSPE, sodium salt, N-(Carbonyl-methoxypolyethyleneglycol 5000)-MPEG-5000-DPPE, sodium salt, N-(Carbonyl-methoxypolyethyleneglycol 750)-MPEG-750-DSPE, sodium salt, N-(Carbonyl-methoxypolyethyleneglycol 2000)-MPEG-2000-DSPE, sodium salt.

In a preferred embodiment the amount of phospholipid in the compositions according to the present invention, by weight based on the total volume of the composition (wt./vol.), is at least 0.064%, preferably at least 0.085%, more preferably at least 0.25%, even more preferably at least 0.3%, even more preferably at least 0.35%, most preferably at least 0.5%.

In another preferred embodiment the amount of phospholipid in the compositions according to the present invention, by weight based on the total volume of the composition (wt./vol.), is less than or equal to 3.4%, preferably less than or equal to 3.3%, more preferably less than or equal to 2.6%, even more preferably less than or equal to 2.3%, even more preferably less than or equal to 2.2%, most preferably less than or equal to 2.1%

Most highly preferred compositions comprise phospholipid in an amount (wt./vol.) within the range of 0.7% to 2.0%, preferably within the range of 1.0% to 1.3%, most preferably 1.02%. Compositions comprising phospholipid within these limits show excellent physical stability and pH stability throughout storage.

In a highly preferred embodiment, the phospholipid component comprises a mixture of phospholipids, such as 79% phosphatidylcholine, 18% phosphatidylethanolamine, 2% sphingomyelin and 1% lysophosphatidylcholine.

In a preferred embodiment the source of the phospholipid emulsifier of the present invention is lecithin, preferably egg lecithin. According to the United States Pharmacopoeia (USP), lecithin is a non-proprietary name describing a complex mixture of acetone-insoluble phospholipids, which consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol, combined with various amounts of other substances such as triglycerides, fatty acids, and carbohydrates.

Soy lecithin and egg lecithin (including hydrogenated versions of these compounds) have a long history of safety in biological systems, possess combined emulsification and solubilization properties, and tend to be metabolized in vivo into innocuous substances more rapidly than most synthetic surfactants. Commercially available soya lecithin/phospholipids are the Centrophase and Centrolex products (Central Soya), Phospholipon (Phospholipid GmbH, Germany), Lipoid (Lipoid GmbH, Germany), EPIKURON (Degussa), and PL90 (Fresenius Kabi, Sweden). In a highly preferred embodiment the source of phospholipid is egg lecithin.

In certain embodiments the total amount of emulsifier, including phospholipid, in the compositions of the present invention is within a range of 0.05% to 4.8% by weight based on the total volume of the composition (wt./vol.).

In preferred embodiments the amount of lecithin (wt./vol.) according to the present invention, is less than or equal to 4.2%, preferably less than or equal to 3.4%, more preferably less than or equal to 2.9%, even more preferably less than or equal to 2.6%, even more preferably less than or equal to 2.5%, most preferably less than or equal to 2.0%.

In certain embodiments the total amount of lecithin, especially egg lecithin, (wt./vol.) is greater than or equal to 0.08%, more preferably greater than or equal to 0.1%, even more preferably greater than or equal to 0.15%, more preferably greater than or equal to 0.2%, even more preferably greater than or equal to 0.3%, even more preferably greater than or equal to 0.35%, most preferably greater than or equal to 0.6%,

Most highly preferred compositions comprise egg lecithin in an amount (wt./vol.) within the range of 0.8% to 2.3%, preferably 0.9% to 1.5%, more preferably 1.0% to 1.3%, even more preferably 1.2%.

In one embodiment the egg lecithin comprises 60-80% wt./wt., preferably 67% wt./wt. phospatidyl choline; 10-20% wt./wt., preferably 15% wt./wt phospatidlylethanolamine; ≤3% wt./wt, preferably 2% wt./wt sphingomyelin; and ≤3% wt./wt, preferably 1% wt./wt lysophosphatidylcholine. "Egg lecithin PL90" (Fresenius Kabi AB) is one example of an egg lecithin having such a phospholipid content.

In one embodiment the compositions of the present invention comprise no more than 1.5% wt/wt, preferably no more than 1.2% wt/wt, more preferably no more than 0.8% wt/wt, and most preferably no more than 0.4% wt/wt of polyethylene glycol 15-hydroxystearate. In another embodiment the compositions of the present invention comprise no more than 1.5% wt/wt, preferably no more than 1.2% wt/wt, more preferably no more than 0.8% wt/wt, most preferably no more than 0.4% wt/wt polyethylene glycol ester and/or polyethylene-propylene glycol

Co-surfactant

The compositions according to the present invention optionally comprise a co-surfactant. Without being bound by theory, co-surfactants are thought to stabilize lipid

droplets during formation of the emulsion, thus influencing emulsion droplet size and stability of the final emulsion composition. Co-surfactants suitable for use in compositions of the present invention are those that prevent flocculation and/or coalescence of the lipid emulsion. Exemplary co-surfactants include, but are not limited to, cholesterol, oleic acid, oleate, Tween80 (PEG-sorbitan monooleate), HCO-60, Solutol H15 (polyoxyethylene-660-hydroxystearate), PEG-400 (polyethylene glycol), Pluronic F68 (BASF), Cremophor EL (polyoxyethylene-35-ricinoleate), or the salt of a bile acid, such as deoxycholic acid. In other embodiments the co-surfactant is selected from the group consisting of C_{12}-C_{22} fatty acids, salts thereof, and/or mixtures thereof, preferably from C_{16}-C_{20} fatty acids, salts thereof, and/or mixtures thereof, most preferably from C_{18} fatty acids, salts thereof, and/or mixtures thereof. In highly preferred embodiments the fatty acid is mono-unsaturated.

In some embodiments the co-surfactant may be present in compositions of the present invention in an amount (wt./vol.) greater than or equal to 0.005 %, preferably greater than or equal to 0.01%, more preferably greater than or equal to 0.02%. In other embodiments the co-surfactant may be present in compositions of the present invention in an amount (wt./vol.) less than or equal to 4%, preferably less than or equal to 1%, more preferably less than or equal to 0.04%. In a preferred embodiment the co-surfactant is selected from the group consisting of long-chain fatty acids, such as palmitic acid, oleic acid or stearic acid, or the alkali salts thereof. Oleate and/or oleic acid, particularly sodium oleate, are highly preferred co-surfactants.

In certain embodiments, wherein the co-surfactant is oleate and/or oleic acid, the co-surfactant is present in an amount (wt./vol.) equal to or greater than 0.005%, preferably equal to or greater than 0.01%, even more preferably equal to or greater than 0.02%. In certain embodiments, wherein the co-surfactant is oleate and/or oleic acid, the co-surfactant is present in an amount (wt./vol.) less than or equal to 0.5%, preferably less than or equal to 0.2%, more preferably less than or equal to 0.1%, most preferably less than or equal to 0.05%.

In a highly preferred embodiment the co-surfactant is sodium oleate and is present in an amount of 0.03% wt./vol.

The compositions of the present invention are preferably suitable for parenteral infusion, preferably intravenous infusion, over prolonged periods. A typical duration of administration may be, e.g. 3-7 days. In preferred embodiments, the concentration of

certain co-surfactants must therefore be kept to a minimum to prevent side effects such as irritation, cytochrome P450 inhibition, etc. In a preferred embodiments Pluronic F68 (poly(ethyleneglycol)-13-poly(propylene glycol co-propylene glycol) is present in an amount less than 0.7% (wt./wt.), preferably less than 0.5% (wt./wt.). In another preferred embodiment Solutol-HS (Macrogol-15-hydroxystearate) is present in an amount less than 1.2% (wt./wt.), preferably less than 1% (wt./wt.).

Osmotic agent

The compositions according to the "Progestogen/oil embodiment" of the present invention suitably comprise an osmotic agent and/or a tonicity modulator. Preferably, the latter compositions have an osmolality in the range of 200-1000 mOsm/kg.

In accordance with a preferred embodiment of both the "progestogen/oil embodiment" and the "progesterone embodiment" the compositions according to the present invention are isotonic and iso-osmotic. The compositions of the present invention advantageously have an osmolality of 220-600 mOsm/kg, most preferably 230-360 mOsm/kg.

Suitable osmotic and/or tonicity modulating agents include potassium or sodium chloride, trahalose, sucrose, sorbitol, glycerol, glucose, xylitol, mannitol, polyethylene glycol, propylene glycol, albumin, amino acid and mixtures thereof. In certain embodiments, an osmolality of 270 to 330 mOsm/kg, preferably 280 to 300 mOsm/kg, is achieved with an agent that also increases osmotic pressure, such as glycerol, dextrose, lactose, sorbitol or sucrose.

In a preferred embodiment the osmotic agent is a physiologically acceptable polyol, such as glycerol, sorbitol or xylitol. In a preferred embodiment the osmotic agent is glycerol.

The osmotic agent and/or tonicity regulating agent of compositions of the present invention is generally used in a concentration that does not have adverse biological effects. The final product is preferably isotonic so as to allow infusion of the emulsion through either a central or peripheral venous catheter.

In preferred embodiments wherein glycerol is the osmotic agent, glycerol is present in a concentration (wt./vol.) greater than 1%, preferably greater than 2%, more preferably greater than 2.3%. In other preferred embodiments glycerol is present at a concentration (wt./vol.) of less than 5%, preferably less than 3%, more preferably less

than 2.7%. In a highly preferred embodiment the emulsions of the present invention comprises 2.5% glycerol.

pH regulating agent

The compositions according to the present invention have a pH within the range of pH 6.0 to pH 9.0, preferably pH 6.5 to pH 8.5, most preferably pH 7.0 to 8.0. The pH of the compositions may be adjusted by methods known in the art, e.g. through the use of an appropriate base that neutralizes the negative charge on the fatty acids, through the use of an appropriate buffer, or a combination thereof. A variety of bases and buffers are suitable for use with the emulsions of the present invention. One skilled in the art will appreciate that the addition of buffer to the emulsion will affect not only the final pH, but also the ionic strength of the emulsion. High ionic strength buffers may negatively impact the zeta potential of the emulsion and are, therefore, not desirable. In a preferred embodiment, the pH is adjusted to the desired value by addition of 1N sodium hydroxide.

Optional Additives

The compositions according to the present invention optionally comprise one or more pharmaceutically acceptable additives, such as acidifying, alkalizing, binding, chelating, complexing, solubilizing agents, antiseptics, preservatives (including antimicrobials and antioxidants), suspending agents, stabilizing agents, wetting agents, viscosity modifying agents, solvents, cryo-protectants, diluents, lubricants or other biocompatible materials. In certain embodiments, such additives assist in stabilizing the colloidal dispersion or in rendering the formulations of the present invention biocompatible.

In one embodiment the compositions of the present invention do not comprise Vitamin E. In another embodiment the compositions of the present invention do not comprise Vitamin C. In another embodiment the compositions of the present invention do not comprise hexasodium phytate. In a preferred embodiment the compositions of the present invention are free of, or substantially free of, alcohol. In one embodiment the compositions of the present invention are free of, or substantially free of, ethanol. In a further embodiment the compositions of the present invention additionally or alternatively do not contain organic solvents.

Preferably, the compositions according to the "Progesterone embodiment" of the present invention comprise less than 2.5% wt./vol. benzyl benzoate.

Both the compositions according to the "Progesterone embodiment" and the compositions according to the "Progestogen/oil embodiment" preferably comprise less than 1% wt./vol. benzyl benzoate. Even more preferably, said compositions comprise less than 1% wt./vol. benzyl alcohols and/or derivatives thereof.

In preferred embodiments the compositions of the present invention do not contain benzyl benzoate, and in highly preferred embodiments do not contain benzyl alcohols and/or derivatives thereof. In one preferred embodiment the compositions of the present invention do not contain cyclodextrin.

Ratios of Emulsion Components

While exemplary amounts of different components that may be included in the compositions of the invention are set forth above, other aspects of the invention relate to ratios of specific components, as discussed below.

Progestogen : Oil ratio

As noted above, the compositions of the invention advantageously have a low oil content, such that minimum lipid is delivered to the subject per unit volume of the composition administered, such that adverse side effects such as hyperlipidemia may be avoided. Moreover, in some embodiments, the compositions achieve improved progestogen solubility in oil, whilst maintaining, or improving, the chemical stability and/or physical stability of the emulsions, such that higher doses of progestogen can be delivered to a subject per unit oil.

The compositions according to the "Progesterone embodiment" typically contain progesterone and oil in a ratio of progesterone to total oil component (wt./wt.) of at least 1:35, more preferably of at least 1:33, even more preferably of at least 1:32.

According to particularly preferred embodiments of the "Progestogen/oil embodiment" and of the "Progesterone embodiment", the ratio of progestogen to total oil component (wt./wt.) is at least 1:31. Typically, the latter ratio does not exceed 1:22, more preferably, it does not exceed 1:23, more preferably it does not exceed 1:24, more preferably it does not exceed 1:25, more preferably it does not exceed 1:26, more preferably it does not exceed 1:27, even more preferably it does not exceed 1:28 and most preferably it does not exceed 1:29. In one embodiment, the ratio of progestogen to

oil component is between 1:32 and 1:25 (wt./wt.), even more preferably 1:31 to 1:29 (wt./wt.).

In preferred embodiments, the compositions of the present invention comprise progestogen, preferably progesterone, in an amount expressed as %wt./wt. of the oil of greater than 1% preferably greater than 1.5%, more preferably greater than or equal to 2%, especially greater than or equal to 2.2%. In even more preferred embodiments the progestogen is present in an amount greater than 2.5%, even more preferably greater than 3 %, most preferably greater than 3.2% wt./wt. of the oil.

Phospholipid : Oil ratio

It was found that excess amounts of phospholipid in oil-in-water compositions can lead to an increase in phospholipid degradation products following autoclaving and/or storage, causing a drop in pH, which in turn negatively impacts upon emulsion stability. Furthermore, excess phospholipid may lead to an increase in the number of large fat-free micelles in the compositions, and hence an undesirable increase in $PFAT_5$ value. On the other hand, compositions with too low a level of phospholipids do not show sufficient emulsion droplet stability to withstand sterilization by autoclaving and storage. Compositions of the present invention have an optimized level of oil and phospholipid such that an optimum particle size distribution and superior physical stability is achieved, whilst a pH within the desired range is maintained throughout heat-sterilization and storage.

In one embodiment, the compositions of the present invention comprise phospholipid in an amount expressed as % wt./wt. of the oil, greater than or equal to 6.8%, preferably greater than or equal to 8.4%, more preferably greater than or equal to 12%, even more preferably greater than or equal to 14%, most preferably greater than or equal to 15%.

In one embodiment, the compositions of the present invention comprise phospholipid in an amount expressed as % wt./wt of the oil, less than or equal to 43%, preferably less than or equal to 42.5%, more preferably less than or equal to 26%, even more preferably less than or equal to 25%, most preferably less than or equal to 22%.

In a highly preferred embodiment the phospholipid is present in an amount within the range of 16 to 18% (wt./wt.) of the oil.

In another embodiment, the compositions of the present invention comprise lecithin, preferably egg lecithin, in an amount expressed as % wt./wt of the oil, greater than or equal to 8%, preferably greater than or equal to 10%, more preferably greater than or equal to 13%, even more preferably greater than or equal to 15%, most preferably greater than or equal to 18%.

In one embodiment, the compositions of the present invention comprise lecithin, preferably egg lecithin, in an amount expressed as % wt./wt of the oil,

less than or equal to 50%, preferably less than or equal to 48%, more preferably less than or equal to 40%, even more preferably less than or equal to 33%, most preferably less than or equal to 31%.

In a highly preferred embodiment egg lecithin is present in an amount within the range of 19-21% (wt./wt.) of the oil.

Co-surfactant : oil ratio

In certain embodiments of the present invention, the compositions comprise a co-sufactant, preferably oleate or oleic acid. In one embodiment the co-surfactant is present in an amount expressed as % wt./wt. of the oil, greater than 0.02. Preferably, the concentration of co-surfactant contained in the composition, in an amount expressed as % wt./wt. of the oil, is greater than or equal to 0.08%, preferably is greater than or equal to 0.1%, even more preferably greater than or equal to 0.3%. In another preferred embodiment the concentration of co-surfactant contained in the composition, in an amount expressed as % wt./wt. of the oil, is less than or equal to 2%, preferably less than or equal to 0.9%, even more preferably less than or equal to 0.7%.

In a highly preferred embodiment the co-surfactant is oleate or oleic acid, and is present in an amount of 0.5% of the oil (wt./wt.).

Cosurfactant : Phospholipid ratio

In one embodiment of the present invention, the compositions comprise phospholipid and a co-surfactant, preferably oleate. In this embodiment the co-surfactant and the phospholipid are preferably present in a co-surfactant to phospholipid ratio (wt./wt.) greater than or equal to 1:85, preferably greater than or equal to 1:82, more preferably greater than or equal to 1:68, even more preferably greater than or equal to 1:51, most preferably greater than or equal to 2:85. In this

embodiment the co-surfactant and the phospholipid are preferably present in a co-surfactant to phospholipid ratio (wt./wt.) less than or equal to 1:12, preferably less than or equal to 1:17, more preferably less than or equal to 1:20, even more preferably less than or equal to 1:26, most preferably less than or equal to 1:34.

In a preferred embodiment wherein the co-surfactant is oleate, the co-surfactant to phospholipid ratio (wt./wt.) is within the range of 1:51 to 1:30, preferably 1: 51 to 1:34.

In another embodiment of the present invention, the compositions comprise lecithin and a co-surfactant, preferably oleate. In this embodiment the co-surfactant and the lecithin are preferably present in a co-surfactant to lecithin ratio (wt./wt.) greater than or equal to 1:100, preferably greater than or equal to 1:80, more preferably greater than or equal to 1:70, even more preferably greater than or equal to 1:60, most preferably greater than or equal to 1:50. In this embodiment the co-surfactant and the lecithin are preferably present in a ratio (wt./wt.) less than or equal to 1:15, preferably less than or equal to 1:20, more preferably less than or equal to 3:70, even more preferably less than or equal to 1:30, most preferably less than or equal to 1:40.

In a preferred embodiment wherein the co-surfactant is oleate, and the lecithin is egg lecithin, the co-surfactant to lecithin ratio (wt./wt.) is within the range of 1:60 to 1:30, preferably 1:60 to 1:35.

Progestogen : Phospholipid ratio

In one embodiment, the progestogen is present in an amount less than 58% wt./wt. of the phospholipid, preferably less than 29% wt./wt. of the phospholipid. Preferably, in another embodiment of the compositions according to the present invention the progestogen is progesterone, and the progesterone is present in amount, expressed as a % wt./wt. of the phospholipid, of greater than 7.8%, preferably greater than 9.8%, more preferably greater than 13%, even more preferably greater than 15%.

Preferably, in another embodiment of the compositions according to the present invention the progestogen is progesterone, and the progesterone is present in amount, expressed as a % wt./wt.of the phospholipid, of less than 47%, preferably less than 39%, more preferably less than 26%, even more preferably less than 20%.

In one embodiment of the compositions according to the present invention the progestogen is progesterone and phospholipid is provided by lecithin, the progesterone

and lecithin being present in a wt./wt. ratio of 1:15 to 2:5, preferably 1:12 to1:3, more preferably 1:9 to 2:9, even more preferably 2:15 to 1:6. In a preferred embodiment the progesterone to lecithin ratio (wt/wt) is less than 1:2, preferably less than 1:4.

Progestogen : co-surfactant ratio

In one embodiment, co-surfactant is present in compositions according to the present invention in an amount greater than 2.5% by weight of the progestogen, preferably greater than 5% by weight of the progestogen.

Packaging

The compositions of the present invention are preferably ready-to-use. "Ready-to-use" as used herein means that no further manipulation, such as diluting or mixing together of multiple components is required.

The compositions of the present invention may be provided in sealed packaging. The packaging should be compatible for use with lipid formulations and progestogens. Examples of materials not suitable for packaging of lipid formulations include PVC and DEHP. Suitable packaging which is compatible with lipid formulations includes, but is not limited to, polypropylene-based bags and glass bottles. Conventional glass is a preferred packaging for compositions of the present invention. In a preferred embodiment the compositions is packaged in a sealed container. The container may be overwrapped to provide protection from the physical environment. In one embodiment the composition is packaged in sealed container having a volume of 250ml. In one embodiment the composition is packaged in a sealed container under a headspace of inert gas.

In other embodiments the compositions are packaged in inert containers. In one embodiment the inert containers are light occluded. In another embodiment the container comprises a double-layered wall, and in preferred embodiments, the area between the two layers is filled with an inert gas in order to prevent oxidation.

For prolonged storage the packaging material needs to prevent the diffusion of oxygen from the ambient air towards the compositions of the invention, to prevent the formation of oxygen degradants within the compositions.

In another embodiment the composition is packaged in a unit dose. A unit dose provides sufficient composition either, for administration of a progestogen bolus dose

to a subject, or for administration of the composition over the first hour, preferably first 2 hours, more preferably first 4 hours, of treatment. The unit dose enables rapid and convenient administration of the composition in emergency situations, for example by paramedics in the ambulance, or by first aiders/medics at the location an injury/event occurs. Non-limiting examples of unit dose forms, are injections, pre-filled syringes, glass vials, and/or sealed bags.

In other embodiments, the composition is packaged within a device similar to the insulin-pump device, which is used to administer a continuous infusion therapy, or in a cartridge designed for use with such a device. Exemplary insulin pumps are those marketed by MiniMed and Disetronic. Such pumps may comprise for example, a cannula, a pump reservoir or cartridge in which the composition is stored, pump which may be battery operated, and means of allowing the user to control the exact amount of active being delivered, such as for example, a computer chip.

Highly preferred embodiment

In one highly preferred embodiment of the composition according to the present invention, the compositions comprise 0.15-0.25% wt./vol. progesterone; 5.0 -7.0 % wt./vol. oil; 1.0-1.4% wt./vol. egg lecithin; 80-98.9% wt./vol. water; and has a pH of 6.0-9.0. Compositions according to this highly preferred embodiment represent a compromise between delivery of the most desirable amount of progestogen per unit volume liquid, delivery of the most desirable amount of progestogen per unit oil, physical stability and safety of administration of the emulsion.

Properties of the emulsion

Compositions according to the present invention are milky white in appearance, and present as visually homogenous emulsions.

$PFAT_5$ value

The United States Pharmacopeia (USP) sets the limit for globule size distribution in lipid injectable emulsions (USP 729 - Pharm. Forum. 2005; 3:1448-1453). The limit for fat globules of diameter >5 μm in injectable emulsions, expressed as volume-weighted percentage fat >5 μm, is not exceeding 0.05%, or $PFAT_5$ not exceeding 0.05%. Compositions having a $PFAT_5$ value greater than 0.05% are considered to be unsafe for intraveneous administration. The $PFAT_5$ value of an

emulsion may be influenced by several factors including the total oil content of the emulsion, the choice of co-surfactant, the co-surfactant-to-oil ratio, and the stability of the emulsion droplets to coalescence and/or flocculation.

The compositions according to the present invention have a $PFAT_5$ value of less than or equal to 0.05%, preferably less than or equal to 0.04%, even more preferably less than or equal to 0.02%, most preferably less than or equal to 0.01%.

In one embodiment, 100% of emulsion droplets of compositions of the present invention are less than or equal to 5μm in diameter, and 98% of droplets, preferably 99% of droplets, are less than or equal to 1.5μm diameter. The particle size distribution of droplets greater than 1μm in diameter is determined by Coulter counter (Coulter Multisizer III).

PCS

In one embodiment, the droplets less than or equal to 1 μm in diameter, have a maximum z-average of 350nm, and/or a polydispersion value of no more than 0.25. In a preferred embodiment, the droplets less than or equal to 1 μm in diameter, have a maximum z-average of 250nm, and/or a polydispersion value of no more than 0.20. In an even more preferred embodiment, the droplets less than or equal to than 1 μm in diameter, have a maximum z-average of 220nm, and/or a polydispersion value of no more than 0.15.

Median droplet size

The emulsion droplet size is the key parameter determining the kinetics of emulsion destabilisation, since droplet size directly influences the rate of phenomena such as coalescence, creaming, flocculation, ostwald ripening and ultimately phase separation. Emulsion droplet size is therefore indicative of emulsion stability. Multiple parameters influence emulsion droplet size, including for example the oil-type, surfactant and co-surfactant type, presence of active ingredients, the amount of oil, oil-to-surfactant and oil-to-co-surfactant ratios.

In one embodiment the emulsion droplet particles of compositions according to the present invention have a volume-based median diameter, or D[4,3], of ≤300nm, preferably ≤230 nm, more preferably ≤200nm, even more preferably ≤185nm, and most preferably ≤180nm.

In a highly preferred embodiment the compositions according to the present invention maintain a volume-based median diameter, or D[4,3], of ≤300nm, preferably ≤230 nm, more preferably ≤200nm, even more preferably ≤185nm and most preferably ≤180nm following one, preferably two, even more preferably three rounds of autoclaving at 121°C for 15 mins, and/or following storage at 60°C for 3 weeks, preferably 4 weeks.

Mean droplet size

In one embodiment the emulsion droplet particles of compositions according to the present invention have a volume-based mean diameter, or d(0,5), of ≤300nm, preferably ≤250nm, more preferably ≤200nm, even more preferably ≤185nm, and most preferably ≤180nm.

In a highly preferred embodiment the compositions according to the present invention maintain a volume based mean diameter, or d(0,5), of ≤300nm, preferably ≤250nm, more preferably ≤200nm, even more preferably ≤185nm, and most preferably ≤180nm, following one, preferably two, even more preferably three rounds of autoclaving at 121°C for 15 mins, and/or following storage at 60°C for 3 weeks, preferably 4 weeks.

Span

The Mastersizer "Span" value is a measure of the width or spread of the particle size distribution curve, and is calculated by the formula d(v,0.9)-d(v,0.1))/d(v,0.5) by the Mastersizer unit. In a specific embodiment, compositions of the present invention have a Span of ≤ 2400 such as ≤2100.

Zeta-potential

The zeta potential is related to the stability of the emulsion. Emulsions with a high zeta potential are electrically stabilized while those with low zeta potentials tend to coagulate or flocculate. The zeta potential of emulsions is influenced for example by the choice and amount of surfactant and co-surfactant, the pH of the emulsions, as well as ionic strength of the aqueous solution.

In one embodiment, compositions of the present invention have a zeta potential within the range of, -30 mV to -70 mV, preferably -40 mV to -65 mV, preferably -51

mV to -60 mV. In addition, the zeta potential of the emulsion compositions of the present invention may be -30 mV, -35 mV,- 40 mV, -45 mV , -50 mV, -55mV, -60 mV, -65 mV or -70 mV or higher.

Particulate Matter

In certain embodiments the compositions are free of crystalline solid at ambient temperature (e.g., at one or more temperatures selected from 4°C, from 2°C to 8°C or from 20°C to 25°C). The preparation contains 0-12 particles per ml equal to or greater than 10μm and 0-2 particles per ml equal to or greater than 25μm.

Stability of the Emulsions

Physical Stability

The compositions according to the present invention are surprisingly heat-sterilizable. "Heat-sterilizable" as used herein means that the compositions maintain their physical stability, i.e. do not phase-separate or show signs of flocculation and/or coalescence of the droplets following autoclaving at 121°C for 15 mins.

The compositions according to the present invention are surprisingly storage stable. "Storage stable" as used herein means that the compositions maintain their physical stability, i.e. do not phase-separate or show signs of flocculation and/or coalescence of the droplets following three, preferably four weeks storage at 60°C.

In a highly preferred embodiment, compositions according to the present invention have a $PFAT_5$ value of less than 0.05%, preferably less than or equal to 0.03%, even more preferably less than or equal to 0.02%, most preferably less than or equal to 0.01% following autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

The compositions of the present invention typically do not show any signs of discolouration upon sterilization by autoclaving at 121°C for 15 mins, and/or storage at 60°C for three, preferably 4 weeks.

In another highly preferred embodiment the emulsion droplets of compositions according to the present invention show an increase in volume-based mean diameter, or d(0,5) of no greater than 2%, preferably no greater than 1.5%, even more preferably no

greater than 1% following autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

In another embodiment, the emulsion droplets of compositions according to the present invention show an increase in volume-based median diameter, or D[4,3], of no greater than 2.5%, preferably no greater than 2%, even more preferably no greater than 1.5% following autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

Chemical Stability

In one embodiment, the progestogen content of compositions according the present invention is not reduced more than 10% by wt. progestogen, preferably not more than 5% by wt. progestogen, even more preferably not more than 2% by wt. progestogen following one, preferably two, even more preferably three rounds of autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

In another embodiment, the amount of progestogen-derived degradation/oxidation products in the compositions of the present invention does not exceed 1% by wt. progestogen, preferably 0.7% by wt. progestogen for any individual chemical species, and the total sum of progestogen-derived degradation/oxidation products does not exceed 3% by wt. progestogen, following one, preferably two, even more preferably three rounds of autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

In a particularly preferred embodiment, wherein the progestogen is progesterone, the individual levels of 6-ketoprogesterone, 6-hydroxyprogesterone and 20-hydroxyprogesterone (α- and β-), or δ-6-progesterone do not exceed 1%, preferably do not exceed 0.7% by wt. of progesterone, and the total sum of progesterone degradation products does not exceed 3% by wt. progesterone, following one, preferably two, even more preferably three rounds of autoclaving at 121°C for 15 mins, and/or following three, preferably four weeks storage at 60°C.

Progestogen and progestogen degradation/oxidation products may be quantified by HPLC.

Emulsion components themselves are also subject to chemical instability. For example phospholipids are broken down into non-esterified fatty acids (NEFA) during

storage. This is especially problematic during heat stress, such as autoclaving and/or prolonged storage.

A build up of NEFA negatively impacts upon the pH of the emulsion and the zeta-potential. For these reasons NEFA levels should be limited in compositions of the present invention.

Preferably, the non-esterified fatty acids (NEFA) levels of compositions pre- or post- autoclaving and/or storage following three, or four, weeks at 60°C is ≤12mEq/L, preferably less ≤8mEq/L

Sterility

In a preferred embodiment the compositions according to the present invention are sterile. As used herein "sterile" refers to compositions which pass the sterility test of USP Chapter <71>. Preferred embodiments are compositions which meet the requirements of USP Chapter <85> "Bacterial endotoxin test", and preferably meeting the requirements of the USP Chapter <151> "pyrogen test".

Process

Another aspect of the present invention relates to a method of manufacturing an oil-in-water emulsion composition as defined herein before, said method comprising the steps of:

a) combining water, phospholipid and optionally an osmotic agent to produce an aqueous composition;
b) combining progestogen and oil to produce an oily composition; and
c) combining the aqueous composition and the oily composition followed by homogenization to form a homogenous oil-in-water emulsion.

According to a particularly preferred embodiment, the aqueous composition is homogenized so as to produce a homogeneous suspension, before said aqueous composition is combined with the oily composition. In another advantageous embodiment, the progestogen is added to oil having a temperature of at least 40 °C to facilitate dilution of the progestogen. Preferably, the oily composition is filtered before it is combined with the aqueous composition.

A particularly preferred embodiment of the method of manufacture comprises the steps of:

A) dissolving an osmotic agent in an aqueous medium and stirring;

B) adding surfactant, preferably egg lecithin and stirring;

C) optionally adding a co-surfactant and a pH regulating agent and mixing;

D) dissolving progestogen in oil to form an oil phase;

E) filtering the oil phase, followed by addition of the filtered oil phase to the aqueous phase, and mixing;

F) homogenization to form a homogenous emulsion;

G) optional addition of water;

H) optional addition of sufficient 1N NaOH to adjust the pH to pH 8.0-8.8;

I) optional addition of sufficient aqueous medium to achieve the final volume.

In a particularly preferred embodiment, the homogenization is performed at greater than or equal to 350 bar, preferably greater than or equal to 370 bar.

In particularly preferred embodiments, the methods of manufacturing of the emulsions of the present invention involve the steps of dissolving the egg lecithin in aqueous medium (rather than in oil), adding the oil phase to the aqueous phase (rather than *vice versa*), and homogenization at greater than or equal to 350 bar. These steps are believed to result in emulsions with advantageous properties in terms of particle size and emulsion stability.

In another preferred embodiment, the emulsion is packaged in sealed containers, and sterilized, preferably by heating to at least 121°C (e.g. 121°C to 123°C) for a minimum of 15 mins holding time. The autoclave program is preferably a rotary cycle.

The following provides a detailed example of a method of manufacture. The skilled artisan readily will understand that various modifications and variations can be made, and still fall within the scope of the invention.

Preparation of the pre-emulsion

A clean vessel (vessel A) is filled to about 15% of the bulk volume with aqueous medium. The temperature of the aqueous medium is adjusted to about 55-60°C and the aqueous medium is degassed with nitrogen until its residual oxygen content is ≤ 0,1mg/L. The aqueous medium is kept under a nitrogen atmosphere, with a residual oxygen content of ≤ 0,1mg/L,

throughout the entire duration of the emulsion manufacture process. An osmotic agent is added to the aqueous medium and stirred with a magnetic stirrer for about 3-5 minutes at about 50Hz. Lecithin is added to the aqueous mixture. Co-surfactant and a pH regulator are optionally added, and the mixture is stirred with a high shear mixer (e.g., UltraTurrax) at about 50Hz until a homogenous suspension, with no surfactant visible on the surface of the aqueous phase, is obtained.

Oil Phase: Oil is added to a second vessel (vessel B) and the temperature is adjusted to about 60°C. Progestogen is then dissolved in the heated oil, by stirring with a magnetic stirrer at about 50Hz for about 10min +/- 5min.

The oil phase from vessel B is filtered through a 0.2 μm filter and slowly transferred into the aqueous phase in vessel A. The pre-emulsion is obtained by constant stirring at about 50Hz for about 15 min with a high shear mixer (e.g., Ultra Turrax) until a visually homogenous pre-emulsion is achieved.

Preparation of the Emulsion

The pre-emulsion then undergoes about 4 rounds of homogenization. Each round of homogenization comprises a first step wherein the pre-emulsion is subjected to about 400 +/- 30 bars pressure at a temperature of about 50-80°C (after heat exchange), and a second step wherein the pre-emulsion is subjected to about 100 +/- 30 bars pressure at a temperature of about 55-80°C (after heat exchange).

The emulsion is filtered through a 10μm filter into a clean storage tank, containing sufficient aqueous medium to give a volume of emulsion equal to about 90% of the final volume. The aqueous medium is degassed with nitrogen until the residual oxygen reaches ≤ 0.1 mg/L, and is maintained under a layer of nitrogen. The emulsion is cooled to about 25 – 30°C. A pH regulator is optionally added to achieve a pH of 8.0-8.8. Additional aqueous medium may be added to bring the emulsion to the final concentration.

Filling

The emulsion is transferred to a filling machine where it is transferred into packaging and sealed, such as in glass bottles. The filling device is flushed with and stored under nitrogen. A stream of nitrogen is blown into the packaging prior to filling, and during the filling process, such that the oxygen content in the packaging remains ≤

0.1mg/l. In a preferred embodiment about 255 +/- 1.5ml of emulsion is added to each unit of packaging. The filled packages then undergo evacuation. In a preferred embodiment the packages undergo 4 rounds of air evacuation, each round consisting of 0.5 seconds of air evacuation followed by 0.5 seconds of gassing nitrogen, and a final vacuum value of 0.60 bar (0.40 absolute bar) is achieved. The packages are stoppered, preferably with a rubber stopper (e.g. Stelmi RG6720 halobutyle stoppers).

The packaged emulsion is sterilized by autoclaving within a maximum of about 16 hours holding time (i.e. within about 16 hours post-filling). The autoclaving process involves heating to about 121°C (about 121°C to about 123°C) for a minimum of about 15 mins holding time. The autoclave program is preferably a rotary cycle. The autoclaving process may be carried out from one to three times. Following sterilization the bottles are visually checked for signs of free fat droplets. The emulsion is stored at about 15°C to about 25°C.

Method of Treatment

The pharmaceutical emulsions of the present invention may be administered parenterally, preferably intravenously or intra-arterially, to subjects for therapeutic or prophylactic use. In a preferred embodiment the subject is a mammal, more preferably a human.

The formulations have neuro-protective and/or neuro-regenerative properties. The formulations are useful in the treatment or prevention of nervous system disorders or conditions. Exemplary disorders and conditions include, but are not limited to, central nervous system (CNS) disorders or conditions, spinal chord injury, traumatic brain injury, mild head injury, including concussion characterized by a temporary loss of brain function, pediatric brain injury, degenerative disorders of the CNS such as Parkinson's disease, dementia, including Alzheimer's disease, demyelinating conditions such as multiple sclerosis and chronic, diabetic peripheral neuropathology.

Other exemplary disorders and conditions include ischemic neurological conditions, such as ischemic CNS injury, stroke, including ischemic stroke, hemorrhagic stroke and transient ischemic attacks, and neurocognitive impairments attributed to cardiopulmonary bypass during cardiac surgery, for example post-perfusion syndrome. Further examples include asphasia, sleep disorders, and anxiety disorders such as post-traumatic stress disorder.

The formulations are also useful to provide relief of symptoms associated with the above-listed disorders, such as restoring cognitive function, restoring sleep patterns, normalizing mood disorders, etc. The formulations of the present invention are also useful to treat post-traumatic stress disorders.

In one embodiment the present invention relates to methods of treating a mammalian subject with a traumatic CNS injury, more particularly, a traumatic brain injury (TBI). The methods comprise treatment of a TBI in a mammalian subject by administering to the subject in need thereof a pharmaceutical composition according to the present invention, such that a therapeutically effective concentration of progestogen is delivered. In a preferred embodiment the mammalian subject is a human. The method of the present invention comprises parenterally administering the progestogen-comprising pharmaceutical compositions of the present invention to a subject having a traumatic CNS injury, more particularly, a TBI. In accordance with the method of the present invention, the pharmaceutical composition is used to promote a positive therapeutic response with respect to the traumatic CNS injury.

TBI is physical injury to brain tissue that temporarily or permanently impairs brain function. Diagnosis is suspected clinically and may be confirmed by imaging (primarily CT). Clinical manifestations vary markedly in severity and consequences. Injuries are commonly categorized as open or closed. Open injuries involve penetration of the scalp and skull. Closed injuries typically occur when the head is struck, strikes an object, or is shaken violently, causing rapid brain acceleration and deceleration. Accordingly, the compositions of the invention can be used to treat a TBI, including, blunt traumas (i.e. closed injuries), as well as, penetrating traumas. By "treatment" is intended any improvement in the subject having the traumatic CNS injury including both improved morphological recovery (i.e., enhanced tissue viability) and/or behavioral recovery. The improvement can be characterized as an increase in either the rate and/or the extent of behavioral and anatomical recovery following the traumatic CNS injury. Accordingly, a “positive therapeutic response” includes both a complete response and a partial response. Various methods to determine if a complete or a partial therapeutic response has occurred are discussed in detail in patent applications WO2006/102644, WO2006102596, and WO2008/039898.

By "therapeutically effective amount" is meant a concentration of progestogen that is sufficient to elicit a therapeutic effect.

Thus, the concentration of a progestogen in an administered dose unit in accordance with the present invention is effective in the treatment or prevention of neuronal damage that follows a traumatic injury to the CNS and hence, elicits a neuroprotective effect. Neurodegeneration is the progressive loss of neurons in the central nervous system. As used herein, "neuroprotection" is the arrest and/or reverse of progression of neurodegeneration following a traumatic CNS injury. The therapeutically effective amount will depend on many factors including, for example, the specific activity of the progestogen, the severity and pattern of the traumatic injury, the resulting neuronal damage, the responsiveness of the patient, the weight of the patient, along with other intra-person variability, the mode and/or method of administration, and the progestogen formulation used.

The progestogen-comprising emulsion compositions of the present invention may be administered using any acceptable method known in the art, including intravenous (IV) injection, intramuscular (IM) injection, or subcutaneous (SC) injection. In specific embodiments of the invention, the pharmaceutical composition comprising progestogen is administered by IV injection. When administered intravenously, the pharmaceutical composition comprising the progestogen can be administered by infusion over a period of 1 to 144 hours. In some embodiments, infusion of the progestogen occurs over a period of 24 to 72 hours, over a period of 48 to 96 hours, or over a period of 24 to 144 hours. In a preferred embodiment the infusion of the progestogen occurs over a period of 96 to 120 hours.

In one embodiment of the present invention, the composition is administered via parenteral, preferably intravenous administration, in a total dose of 0.1 ng to 100 g per kg of body weight, 10 ng to 50 g per kg of body weight, from 100 ng to 1 g per kg of body weight, from 1 μg to 100 mg per kg of body weight, from 1mg to 90 mg per kg of body weight, from 2mg to 80 mg per kg of body weight; and from 3mg to 70 mg per kg of body weight. Alternatively, the amount of progestogen administered to achieve a therapeutic effective dose is 0.1 ng, 1 ng, 10 ng, 100 ng, 1 μg, 10 μg, 100 μg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 15mg, 20 mg, 25mg, 30 mg, 35mg, 40 mg, 45 mg, 50 mg, 55mg, 60 mg, 65mg, 70 mg, 75mg, 80 mg, 85mg, 90 mg, 95mg, 100 mg, 500 mg per kg of body weight or greater. In a preferred embodiment progestogen is administered intraveneously, in a total dose of between 50mg and 90mg per kg of body weight.

Progestogen may be administered once or several times a day. The duration of the treatment may be once per day for a period of 1, 2, 3, 4, 5, 6, 7 days or more. The daily dose can be administered either by a single dose in the form of an individual dosage unit or several smaller dosage units or by multiple administration of subdivided dosages at certain intervals. Subsequent dosage units can be administered any time following the initial administration such that a therapeutic effect is achieved. For instance, additional dosage units can be administered to protect the subject from the secondary wave of edema that may occur over the first several days post-injury. In a preferred embodiment, the first dosage unit is administered no later than from 8 hours post-injury.

In specific embodiments of the invention, the progestogen is administered in a constant dosing regimen. By "constant dosing regimen" is meant that the progestogen is administered in a constant total hourly infusion dose of progestogen over the course of treatment. In other embodiments of the invention, the therapy is administered in a "two-level dosing regimen." By "two-level dosing regimen" it is meant that the composition is administered during two dosing time periods. In one embodiment, the total hourly dose of progestogen administered during the first time period of the two-level dosing regimen is a higher total infusion dose of progestogen per hour than that given during the second time period of the two-level dosing regimen. In a specific embodiment, a continuous dose of 0.71mg/kg/hr is administered intravenously during the first time period of the two-level progestogen dosing regimen, and a dose of 0.5mg/kg/hr is given during the second time period of the two-level progestogen dosing regimen. In a highly specific embodiment the first time period of the two-level dosing regimen has a duration of 1 hour, and the second time period has a total duration of 120 hours.

The present method of treatment typically achieves a final serum level of progestogen in the subject of of 100 ng/ml to 1000 ng/ml, 1100 ng/ml to 1450 ng/ml, 100 ng/ml to 250 ng/ml, 200 ng/ml to 350 ng/ml, 300 ng/ml to 450 ng/ml, 350 ng/ml to 450 ng/ml, 400 ng/ml to 550 ng/ml, 500 ng/ml to 650 ng/ml, 600 ng/ml to 750 ng/ml, 700 ng/ml to 850 ng/ml, 800 ng/ml to 950 ng/ml, 900 ng/ml to 1050 ng/ml, 1000 ng/ml to 1150 ng/ml, 1100 ng/ml to 1250 ng/ml, 1200 ng/ml to 1350 ng/ml, 1300 ng/ml to 1500 ng/ml. In specific embodiments, the serum level of progestogen comprises 100 ng/ml, 250 ng/ml, 300 ng/ml, 350 ng/ml, 360 ng/ml, 370 ng/ml, 380 ng/ml, 390 ng/ml,

400 ng/ml, 410 ng/ml, 420 ng/ml, 430 ng/ml, 440 ng/ml, 450 ng/ml, 500 ng/ml, 750 ng/ml, 900 ng/ml, 1200 ng/ml, 1400 ng/ml, or 1600 ng/ml. The serum concentration progestogen can be determined by calculating the area under the curve (AUC) over time following IV administration of the reference composition to a subject, as described in WO2006102596.

In further embodiments of the present invention, at least one additional neuroprotective agent can be combined with the progestogen (either as part of the same composition or in a separate composition) to enhance neuroprotection following a traumatic CNS injury. Such agents include, for example, Vitamin D, and/or compounds that reduce glutamate excitotoxicity and enhance neuronal regeneration. Such agents may be selected from, but not limited to, the group comprising growth factors. By "growth factor" is meant an extracellular signaling molecule that stimulates a cell to grow or proliferate. When the progestogen is administered conjointly with other pharmaceutically active agents, (i.e., other neuroprotective agents) lesser concentrations of progestogen may be therapeutically effective.

Having now generally described this invention, the same will be better understood by reference to certain specific examples which are included herein for purposes of illustration only, and are not intended to be limiting of the invention, unless specified.

EXAMPLES

Example 1 – Preferred Embodiment

The formulation of example 1 is a 6% oil emulsion composition, comprising 0.2% progesterone and 1.2% egg lecithin. The phospholipid is present in an amount of 17% of the oil (wt./wt.), and the progesterone to oil ratio is 1:30 (wt./wt.)

Table I

Material	Quantity
Water for Injection	Ad 400L
Egg lecithin PL90	4.77kg
Glycerol	9.98kg
Oleic acid	0.12kg
NaOH 1M	470ml
Soy bean oil	23.97kg
Progesterone	0.81kg

The emulsion of Table I was manufactured as follows. Components, mixtures and the finished emulsion were kept under nitrogen gas, and at a temperature of 55-60°C, unless otherwise indicated.

180L of water for injection (w.f.i.) was added to a first vessel, warmed to 58°C, whilst mixing at 50Hz and degassed with nitrogen until a residual oxygen concentration of ≤ 0.1 mg/L was obtained. 9.98kg glycerol (anhydrous Glycerol, Axelis, Austria) was added to the water and mixed for 5 minutes at 50Hz. 23.97kg of soybean oil (Fresenius Kabi, Sweden) was added to a second vessel, stirred at 50Hz and warmed to 58°C. 0.81kg of progesterone (micronized progesterone by Proquina, Mexico) was added to the heated soybean oil under constant stirring. 4.77kg egg lecithin (PL90, Fresenius Kabi, Sweden) was added to the warmed water -glycerol mixture, followed by 0.12kg oleic acid (Merck KGaA) and 470ml NaOH 1M (Merck KGaA). The contents of the first vessel were stirred with Ultra Torrax (UT) at 50Hz until a homogenous suspension was obtained (about 15 mins).

When the oil phase in the second vessel had reached a temperature of 56°C and the progesterone was fully dissolved, the mixture was stirred for a further 15 mins. The oil-phase was filtered through a 0.2μm filter, and slowly transferred into the first vessel (over a period of about 18mins). Two 5L volumes of water for injection warmed to 58°C were used to rinse the second vessel, prior to their addition to the first vessel. An additional 110mL of NaOH 1M was added to bring the pH to pH8.0. The pre-emulsion was stirred with UT at 50Hz for 15minutes and a visually homogenous pre-emulsion was achieved.

The pre-emulsion then underwent 4 rounds of homogenization each round lasting about 70mins, and each round consisting of 2 homogenization steps. The first round consisted of a first step at 418 bar, and a second step at 108 bar. The second consisted of a first step at 407 bar, and a second step at 103 bar. The third round consisted of a first step at 411 bar, and a second step at 102 bar. The final round consisted of a first step at 410 bar, and a second step at 101 bar. The temperature of the pre-emulsion was between 50°C and 67°C inclusive throughout.

150L w.f.i. was added to a storage tank, heated to 27.9°C and degassed with Nitrogen gas to reach a residual oxygen concentration of ≤ 0.1 mg/L. The emulsion was filtered through a 10μm filter into the w.f.i. containing storage tank. The emulsion was cooled to 27°C, sampled, and sufficient water (23L) was added to bring the emulsion to final concentration. The final emulsion was degassed to a residual oxygen content of ≤ 0.1 mg/L, and stored under nitrogen gas at 27°C for 11 hours prior to filling of the emulsion into bottles. The emulsion was filled into glass bottles, and sealed, giving packaged unit doses of about 250ml. The amount of oxygen in the emulsion was kept at a level of ≤ 0.1 mg/L throughout the filling process, by gassing the bottles with nitrogen prior to filling, and gassing the emulsion and the bottles during filling.

The bottles were sterilized by autoclaving on a rotary cycle at 121°C for a holding time of 15mins (basket with samples rotating at 4 rpm).

In the following table data is presented on the physical and chemical characteristics of the emulsion of example 1 prior to sterilization, following sterilization by autoclaving at 121°C for 15 mins, and following storage of the autoclaved emulsion at 60°C for 3 weeks, and for 4 weeks.

EXAMPLE 1	NON-STERILE	STERILIZED	3 WEEKS, 60°C	4 WEEKS, 60°C
PCS Z-AVERAGE [NM]	215	214	217	220
PCS POLY	0.11	0.09	0.10	0.12
MASTERSIZER D[4,3] [µM]	0.174	0.175	0.176	0.173
MASTERSIZER SPAN	1.650	1.658	1.656	1.651
MASTERSIZER UNIFORMITY	0.521	0.524	0.522	0.524
MASTERSIZER D(0,5) [µM]	0.147	0.148	0.149	0.146
COULTER COUNTER % ≤ 1,5µM	99.5	99.3	100	99
COULTER COUNTER % ≤ 5µM	100	100	100	100
ACCUSIZER [%] (USP 729)	0.01	0.01	0.00	0.00
APPEARANCE	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
PH-VALUE	8.5	7.9	6.6	7.0
PEROXIDE VALUE [MEQU/L]	0.01	0.04	0	0.2
NEFA [MEQU/L]	1	2	8	6
LPC [%]	1.9	2.8	16	13

The emulsions of Example 1 have a particle size distribution representative of stable and safe to administer compositions. The Accusizer values show that the $PFAT_5$ value is well within the limit of <0.05%. The mastersizer data show that the emulsions have low mean (d(0,5)) and median (D[4,3]) particle size values, which are representative of stable emulsions.

Furthermore, the particle size values do not show any significant increases following heat-sterilization or storage at 60°C for 3 or 4 weeks. The emulsion compositions of Example 1 also exhibit NEFA, LPC and pH values within specification following sterilization and storage.

Comparative Example 2 – Progesterone-containing Oil-in-Water Emulsions

The formulation of Table II is a 20% oil emulsion composition, wherein the phospholipid is present in an amount of 6% of the oil (wt./wt.), and the progesterone is

present in an amount of 3% of the oil (wt./wt.). The 20% emulsion formulation of Table II was further diluted with either saline or water to produce 5% oil emulsions, comprising 0.26% phospholipid and 0.15% progesterone. The 5% emulsions produced with saline are non-homogenous (i.e. they phase-separate), and 5% emulsions produced with water have a very low osmolality. The formulations of example 2 therefore fall outside the scope of the claims of the present invention.

Table II

Material	Per 2000ml
Water for Injection	Ad 2000ml
Egg lecithin	24g
Glycerol	50g
Sodium oleate	0.6g
Soybean oil	400g
Progesterone	12g

A. The 20% oil emulsion formulation of Table II (Example 2A) was manufactured by the following method. 400g soybean oil was heated in a vessel to about 70°C. 12g progesterone was added to the soybean oil and the mixture was stirred using a magnetic stirrer. 400ml water was placed in a separate vessel and heated to about 70°C. 50g glycerol was added to the water phase and dissolved by high shear mixing. 24g egg lecithin was added to the glycerol solution under high shear mixing.

The oil phase was slowly added to the aqueous phase under constant high shear mixing. 0.6g sodium oleate was added and the solution was further mixed. The resultant pre-emulsion underwent 4 rounds of homogenization at 400 bar (Minilab homogenizer). The emulsion was left to cool to 25°C, the final volume was adjusted to 100% (2L), and the emulsion was stirred. The emulsion was filtered through a 5 μm filter, and filled into 50ml glass bottles. The bottles were sterilized by autoclaving at 121°C for a holding time of 15mins.

B. The 5% oil emulsion of example 2B was made by diluting 500ml of the non-autoclaved emulsion of Example 2A with 1500mL 0.9% NaCl. Upon dilution with the 0.9% NaCl, the emulsions phase-separated.

C. The emulsion of example 2C was made by diluting 500ml of the non-autoclaved emulsion of Example 2A with 1500mL water for injection. The emulsion was filtered through a 5 μm filter. The emulsion was filled into 50ml glass bottles. The bottles were sterilized by autoclaving at 121°C for a holding time of 15mins, and stored for 3 weeks at 60°C.

EXAMPLE 2	A NON STERILE	A STERILIZED	B NON-STERILE	C NON-STERILE	C STERILIZED	C 3 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	PHASE SEPARATED	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
visual control	NO PARTICLES	NO PARTICLES	-	NO PARTICLES	NO PARTICLES	NO PARTICLES
PCS Z-Average [nm]	285.0	287.8	-	286.7	286.2	286.0
PCS Poly	0.10	0.12	-	0.10	0.09	0.11
Mastersizer D[4,3] [μm]	0.348	0.355	-	0.346	0.352	0.348
MASTERSIZER SPAN	1.462	1.395	-	1.474	1.426	1.470
MASTERSIZER UNIFORMITY	0.459	0.438	-	0.463	0.448	0.462
MASTERSIZER d(0.5) [μM]	0.309	0.317	-	0.307	0.313	0.308
ACCUSIZER [%] (USP 729)	0.21	0.85	-	0.27	0.24	0.18
PH-VALUE	8.2	7.7	-	7.8	7.4	6.1
OSMOLALITY MOSM	307	307	292	68	68	68

The 20% emulsion (2A) compositions have a $PFAT_5$ value that exceeds the limits set by USP, chapter <729>. Furthermore, the 20% compositions have larger D[4,3] and d(0,5) values than compositions of the present invention and these values increase upon autoclaving indicating physical instability.

Dilution of 20% oil emulsions of Example 2A with 0.9% NaCl caused the resulting emulsions (2B) to phase-separate. Dilution of the 20% oil emulsions of

Example 2A with water to give 5% oil emulsions (2C) gave white homogenous emulsions, with a very low osmolality. Analysis of the physiochemical properties of emulsions 2C revealed that they have a $PFAT_5$ value that far exceeds the maximum value set by USP, chapter <729>. Furthermore, the median particle size and mean particle size values are larger than the equivalent values observed for the emulsions according to the present invention, and they increase upon autoclaving, indicating poor physical stability.

Comparative Example 3- Progesterone- and Estradiol- containing Oil-in-Water Emulsions

The formulation of Table III is a 20% oil emulsion composition, wherein the phospholipid is present in an amount of 6% of the oil (wt./wt.), and the progesterone is present in an amount of 3% of the oil (wt./wt.). The formulation additionally contains 0.066% Estradiol hemihydrate. The 20% emulsion formulation of Table III was further diluted with either saline or water to produce 5% oil emulsions, comprising 0.26% phospholipid and 0.15% progesterone. The formulations of example 3 fall outside the scope of the claims of the present invention.

Table III

Material	Per 2000ml
Water for Injection	Ad 2000 ml
Egg lecithin	24g
Glycerol	50g
Sodium oleate	0.6g
Soy bean oil	400g
Progesterone	12g
Estradiol hemihydrate	1.32g

A. The emulsion of example 3A was manufactured by the following method. 400g soybean oil was heated in a vessel to 70°C. 12g progesterone and 1.32g

estradiol hemihydrate were added to the soybean oil. The mixtures were stirred using a magnetic stirrer. 400ml water was placed in a separate vessel and heated to 70°C. 50g glycerol was added to the water phase and dissolved by high shear mixing. 24g egg lecithin was added to the glycerol solution under high shear mixing. The oil phase was slowly added to the aqueous phase under constant high shear mixing. 0.6g sodium oleate was added and the solution was further mixed. The resultant pre-emulsion underwent 4 rounds of homogenization at 400 bar (Minilab homogenizer).

The emulsion was left to cool to 25°C, the final volume was adjusted to 100% (2L), and the emulsion was stirred. The emulsion was filtered through a 5 µm filter. The emulsion was filled into 50ml glass bottles. The bottles were sterilized by autoclaving at 121°C for a holding time of 15mins.

B. The emulsion of example 3B was manufactured by diluting 500mL of the non-autoclaved emulsion of Example 2A with 1500ml 0.9% NaCl and stirring. Upon dilution with the 0.9% NaCl, the emulsions phase-separated.

EXAMPLE 3	A NON STERILE	A STERILIZED	B NON STERILE	C NON STERILE	C STERILIZED	C 3 WEEKS, 60°C
APPEARANCE	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	PHASE SEPARATED	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
visual control	NO PARTICLES	NO PARTICLES	-	NO PARTICLES	NO PARTICLES	NO PARTICLES
PCS Z-Average [nm]	281.4	287.2	-	287.3	286.2	288.4
PCS Poly	0.12	0.10	-	0.10	0.11	0.13
Mastersizer D[4,3] [µm]	0.403	0.410	-	0.419	0.404	0.401
MASTERSIZER SPAN	1.757	1.704	-	1.680	1.721	1.702
MASTERSIZER UNIFORMITY	0.652	0.634	-	0.626	0.631	0.609
MASTERSIZER d(0.5) [µM]	0.310	0.316	-	0.324	0.314	0.316
ACCUSIZER [%] (USP 729)	0.80	0.71	-	0.18	0.16	0.51
PH-VALUE	8.3	7.8	-	8.2	7.4	6.4
OSMOLALITY MOSM	394	394	312	75	75	

C. The emulsion of example 3C was manufactured by diluting 500mL of the non-autoclaved emulsion of Example 3A with 1500mL water for injection and stirring. The emulsion was filtered through a 5 μm filter. The emulsion was filled into 50ml glass bottles. Some bottles were sterilized by autoclaving at 121˚C for a holding time of 15mins, and subsequently stored for 3 or 4 weeks at 60˚C.

The 20% emulsion compositions have a $PFAT_5$ value that exceeds the limits set by USP chapter <729>. Furthermore, the 20% compositions have larger D[4,3] and d(0,5) values than compositions of the present invention and these values increase upon autoclaving indicating physical instability.

Dilution of 20% oil emulsions of Example 3A with 0.9% NaCl, caused the resulting emulsions (3B) to phase-separate.

Dilution of the 20% oil emulsions of Example 3A with water to give 5% oil emulsions (3C) gave white homogenous emulsions, with a very low osmolality.

Analysis of the physiochemical properties of emulsions 3C revealed that they have a $PFAT_5$ value that far exceeds the maximum value set by USP chapter <729>. Furthermore, the median particle size and mean particle size values are larger than the equivalent values observed for the emulsions according to the present invention.

Example 4 – Effect of Phospholipid

The following example demonstrates the effect of varying the phospholipid content of emulsion compositions on the properties of the emulsions. The 6% oil emulsions of Table IV were prepared by the method outlined below. The emulsions contained 0.2% progesterone, and either 1.8%, 1.5%, 0.9%, or 0.6% lecithin.

Table IV

EXAMPLE 4	A	B	C	D
Water for Injection	Ad 10L	Ad 10L	Ad 10L	Ad 10L
Egg lecithin	180 g	150 g	90 g	60 g
Glycerol	250 g	250 g	250 g	250 g
Sodium oleate	3 g	3 g	3 g	3 g
Soy bean oil	600 g	600 g	600 g	600 g
Progesterone	20 g	20 g	20 g	20 g
NaOH (1M)	9 ml	9 ml	9 ml	9 ml
NaOH (1M) Ad pH 8.0-8.8	3 ml			

The emulsions of example 4 A-D were prepared by the following method. 600g soybean oil (Fresenius Kabi, Sweden) was added to a vessel and warmed to 58°C.

The oil was kept under an atmosphere of nitrogen gas whilst 20g progesterone (micronized progesterone by Proquina, Mexico) was added to the soybean oil and dissolved by mixing with a magnetic stirrer. WFI was placed in a second vessel and heated to 58°C. 250g glycerol (anhydrous Glycerol, Axelis, Austria) was added to the water phase and dissolved by high shear mixing. The indicated amount of egg lecithin (PL90 by Fresenius Kabi, Sweden) and 3g sodium oleate (Merck KGaA) were added to the water phase.

The oily phase was slowly added to the water phase under constant high shear mixing. 9 ml NaOH was added to the mixture and stirred by high shear mixing.

The pre-emulsion underwent four runs of homogenization, each run comprising 2 stages. The first stage of consisting of 400+/- 30 bar and the second stage consisting of 100+/-30 bar. The emulsion was cooled to 20°C, sufficient water for injection was added to bring the final volume of the emulsion to 100%, and the emulsion was stirred by high shear mixing. Where necessary, sufficient NaOH (1M) was added to adjust the pH of the emulsion (e.g. Emulsion A: 3ml NaOH). The emulsion was filtered through a 10µm filter, and filled into 50ml glass bottles. The bottles were sterilized on a rotary cycle for 15min at 121°C. Sterilization was repeated twice. The bottles were subsequently stored for 3 or 4 weeks at 60°C.

EXAMPLE 4A	NON STERILE	STERILIZED 1 X	STERILIZED 2 X	STERILIZED 3 X	3 WEEKS, 60°C	4 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
VISUAL CONTROL	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES
MASTERSIZER D[4,3] [µM]	0.206	0.206	0.204	0.206	0.202	0.202
MASTERSIZER SPAN	1.895	1.894	1.898	1.896	1.894	1.884
MASTERSIZER UNIFORMITY	0.585	0.585	0.587	0.586	0.586	0.583
MASTERSIZER d(0,5) [µM]	0.169	0.168	0.167	0.168	0.165	0.165
ACCUSIZER [%] (USP 729)	0.02	0.02	0.02	0.03	0.02	0.03
PH-VALUE	8.0	7.7	7.5	7.4	6.6	6.9

EXAMPLE 4B	NON STERILE	STERILIZED 1 X	STERILIZED 2 X	STERILIZED 3 X	3 WEEKS, 60°C	4 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
VISUAL CONTROL	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES
MASTERSIZER D[4,3] [µM]	0.214	0.215	0.213	0.214	0.12	0.217
MASTERSIZER SPAN	1.908	1.909	1.917	1.913	1.914	1.899
MASTERSIZER UNIFORMITY	0.587	0.587	0.590	0.589	0.590	0.583
MASTERSIZER d(0,5) [µM]	0.176	0.176	0.174	0.175	0.174	0.179
ACCUSIZER [%] (USP 729)	0.02	0.02	0.03	0.02	0.02	0.02
PH-VALUE	8.3	7.9	7.6	7.4	6.4	6.5

EXAMPLE 4C	NON STERILE	STERILIZED 1 X	STERILIZED 2 X	STERILIZED 3 X	3 WEEKS, 60°C	4 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
VISUAL CONTROL	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES
MASTERSIZER D[4,3] [µM]	0.228	0.229	0.228	0.229	0.232	0.227
MASTERSIZER SPAN	2.065	2.059	2.069	2.066	2.041	2.069
MASTERSIZER UNIFORMITY	0.633	0.632	0.635	0.635	0.628	0.637
MASTERSIZER d(0,5) [µM]	0.181	0.182	0.180	0.182	0.185	0.80
ACCUSIZER [%] (USP 729)	0.01	0.01	0.03	0.01	0.02	0.02
PH-VALUE	8.2	8.0	7.8	7.6	7.2	6.8

EXAMPLE 4D	NON STERILE	STERILIZED 1 X	STERILIZED 2 X	STERILIZED 3 X	3 WEEKS, 60°C	4 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
VISUAL CONTROL	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES
MASTERSIZER D[4,3] [µM]	0.241	0.240	0.243	0.239	0.247	0.247
MASTERSIZER SPAN	2.135	2.121	2.111	2.145	2.090	2.080
MASTERSIZER UNIFORMITY	0.658	0.654	0.652	0.660	0.646	0.644
MASTERSIZER d(0,5) [µM]	0.189	0.189	0.192	0.187	0.196	0.196
ACCUSIZER [%] (USP 729)	0.00	0.00	0.00	0.01	0.01	0.01
PH-VALUE	8.1	8.1	7.8	7.7	7.7	7.4

Compositions A-D formed white homogenous emulsions with particle size parameters representative of safe to administer, heat and storage stable emulsions. $PFAT_5$ values are well within the acceptable range (≤0.05%). With decreasing lecithin content, a clear trend for increasing span, D[4,3] and d(0,5) values is observed, indicative of decreasing physical stability of the emulsions.

In particular a greater increase in particle size (D[4,3], d(0,5)) is observed in the 0.6% lecithin emulsions (formulation 4D) than in the higher lecithin emulsion formulations.

Example 5 – Effect of Co-surfactant

The following example demonstrates how the absence of co-surfactant content of emulsion compositions affects the properties of the emulsions. The 6% oil emulsions of Table V were prepared by the method outlined below.

Table V

Water for Injection	Ad 1L
Egg lecithin	12 g
Glycerol	25 g
Soy bean oil	60 g
Progesterone	2 g
NaOH (1M) Ad pH 8-8.8	500 µl

The emulsion of example 5 was prepared by the following method. 60g soybean oil (Fresenius Kabi, Sweden) was added to a vessel and warmed to 72°C. The oil was kept under an atmosphere of nitrogen gas whilst 2g progesterone (micronized progesterone by Proquina, Mexico) was added to the soybean oil and dissolved by mixing with a magnetic stirrer. WFI was placed in a second vessel and heated to 65°C. 25g glycerol (anhydrous Glycerol, Axelis, Austria) was added to the water phase and dissolved by high shear mixing. 12g egg lecithin (PL90 by Fresenius Kabi, Sweden) was added to

the water phase. The oily phase was slowly added to the water phase under constant high shear mixing. The pre-emulsion underwent five runs of homogenization, at 600 bar. The emulsion was cooled to 20°C, sufficient water for injection was added to bring the final volume of the emulsion to 100%, and the emulsion was stirred by high shear mixing.

500µl NaOH was added to the mixture to adjust the pH of the emulsion. The emulsion was filtered through a 10µm filter, and filled into 50ml glass bottles. The bottles were sterilized on a rotary cycle for 15 min at 121°C. Sterilization was repeated twice for the samples undergoing stability testing.

EXAMPLE 5	NON STERILE	1 X STERILIZED	2 X STERILIZED	3 X STERILIZED	4 WEEKS, 60°C
Appearance	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS	WHITE, HOMOGENEOUS
visual control	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES	NO PARTICLES
Mastersizer D[4,3] [µm]	0.228	0.228	0.220	0.225	0.227
MASTERSIZER SPAN	1.911	1.893	1.934	1.902	1.893
MASTERSIZER UNIFORMITY	0.592	0.587	0.598	0.589	0.587
MASTERSIZER d(0,5) [µM]	0.187	0.188	0.179	0.185	0.187
ACCUSIZER [%] (USP 729)	0.06	0.06	0.02	0.04	0.03
PH-VALUE	7.8	7.2	7.0	6.8	5.8

The co-surfactant free emulsion compositions produced viable emulsions. The particle size parameters D[4,3], d(0,5), Span and $PFAT_5$ values were slightly elevated relative to emulsions containing co-surfactant (Example 1).

Claims

1. A sterile, ready-to-use, pharmaceutical oil-in-water emulsion composition for parenteral administration comprising:
   - 0.015 to 0.5% wt./vol., preferably 0.05 to 0.4% wt/vol. progesterone;
   - 0.5 to 10% wt./vol. of oil, wherein the oil comprises at least 85% wt./wt. triglyceride;
   - 0.0425 to 4.1% wt./vol., preferably 0.064 to 3.4% wt./vol. of phospholipid;
   - 80-99.4% wt./vol. aqueous medium;

   wherein the composition has an osmolality in the range of 200-1000 mOsm/kg, and wherein the emulsion contains no more than 1.2% wt/wt of polyethylene glycol 15-hydroxystearate.

2. The composition according to claim 1 wherein said progesterone is present in an amount greater than 1 % wt./wt. of the oil, preferably greater than 1.5% wt./wt. of the oil.

3. The composition according to claim 1 or 2, wherein the phospholipid is present in the range of 6.8 – 43% of the oil, preferably 8.4 – 42.5% wt./wt. of the oil, more preferably 12 -26 % wt./wt. of the oil, even more preferably 14-25 % wt./wt. of the oil.

4. The composition according to any one of the preceding claims, wherein said composition contains 0.005-4% wt./vol. of a co-surfactant.

5. The composition of claim 4, wherein the co-surfactant is selected from the group consisting of C_{12}-C_{22} fatty acids, salts thereof, and/or mixtures thereof, preferably from C_{16}-C_{20} fatty acids, salts thereof, and/or mixtures thereof, most preferably from C_{18} fatty acids, salts thereof, and/or mixtures thereof.

6. The composition according to claim 5, wherein the co-surfactant is selected from oleate, oleic acid and combinations thereof, and is present in the range of 0.005-0.5% wt./vol.

7. The composition according to any one of the preceding claims, wherein said composition contains an osmotic agent, preferably glycerol.

8. The composition according to any one of the preceding claims, wherein the oil comprises at least 90%, preferably at least 95% triglycerides.

9. The composition according to any one of the preceding claims wherein the composition is suitable for intravenous administration.

10. The composition according to any one of the preceding claims wherein the composition is packaged in a sealed container under a headspace of inert gas.

11. The composition of any one of the preceding claims comprising;

- 0.15-0.25% wt./vol. progesterone;
- 5 -7 % wt./vol. oil;
- 1.0-1.4% wt./vol. egg lecithin;
- 80-98.9% wt./vol. water;

wherein the composition has a pH of 6.0-9.0.

12. The compositions according to any one of the preceding claims wherein the composition has a $PFAT_5$ value of $\leq 0.05\%$.

13. The composition according to any one of the preceding claims wherein the droplet particles of the dispersed oil phase have a volume based mean diameter of ≤ 300nm, preferably ≤ 250nm, more preferably ≤ 200nm, even more preferably ≤ 185nm, most preferably ≤ 180nm.

14. The composition according to any one of the preceding claims for use in therapeutic or prophylactic treatment of a mammal, said treatment comprising parenteral, preferably intravenous administration of the pharmaceutical emulsion to said mammal.

15. A method of manufacturing a composition according to any one of claims 1-14, said method comprising the steps of:

a. combining water, phospholipid and optionally an osmotic agent to produce an aqueous composition;
b. combining progesterone and oil to produce an oily composition;

c. combining the aqueous composition and the oily composition followed by homogenization to form a homogenous oil-in-water emulsion.

16. The method of claim 15, wherein the combination of step c) is achieved by adding the oily composition to the aqueous composition, followed by homogenizing at greater than or equal to 350 bar.