VESICULAR FORMULATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/235,992, filed August 21, 2009, U.S. Provisional Application No. 61/314,476, filed March 16, 2010, and U.S. Provisional Application No. 61/320,154, filed April 1, 2010, each of which are herein incorporated by reference in their entirety.

1. FIELD OF INVENTION

[0002] The present invention relates to formulations of phospholipids and surfactants and to the use of such formulations for the delivery of fatty acids for the treatment of disorders such as, fatty acid metabolic disorders, including essential fatty acid deficiency; pain or inflammation or osteoarthritis, more specifically for the treatment of deep tissue pain; asthma, bronchospasm, atherothrombatic cardiovascular disorders, avenous thrombatic disorders, inflammatory dermatoses disorders (e.g., atopic eczema, dishydrotic hand eczema, plaque type psoriasis, seborrheic eczema, and acne vulgaris), and dysmenorrhea.

2. BACKGROUND

[0003] U.S. Patent No. 6,165,500 to Cevc describes a "preparation for the application of agents . . . provided with membrane-like structures consisting of one or several layers of amphiphilic molecules, or an amphiphilic carrier substance, in particular for transporting the agent into and through natural barriers such as skin and similar materials." Abstract. These transfersomes "consist of one or several components[, m]ost commonly a mixture of basic substances, one or several edge-active substances, and agents []." Col. 5, lines 28-30. According to U.S. Patent No. 6,165,500, "[l]ipids and other amphiphiles are best suited basic substances; surfactants or suitable solvents are the best choice from the point of view of edge-active substances[, and a]ll of these can be mixed with agents in certain proportions depending both on the choice of the starting substances and on their absolute concentration." Col. 5, lines 30-35.

[0004] U.S. Patent Application Publication No. US 2004/0071767 to Cevc et al. describes "formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) based on complex aggregates with at least three amphiphatic components suspended in a . . . pharmaceutically acceptable . . . medium." Abstract. "One of these components is capable of forming stable, large bilayer membranes on its own. The other at least two amphiphatic components, including an NSAID, tend to destabilise such membranes." Paragraph [0002].

[0005] U.S. Patent Application Publication No. US 2004/0105881 to Cevc et al. describes extended surface aggregates, "suspendable in a suitable liquid medium and comprising at least three amphiphats (amphiphatic components) and being capable to improve the transport of actives through semi-permeable barriers, such as the skin, especially for the non-invasive drug application in vivo by means of barrier penetration by such aggregates." Paragraph [0002]. "The three amphiphats include at least one membrane forming compound (MFC), which can form the membrane of [the aggregates], and at least two membrane destabilising compounds (MDC_1 and MDC_2) differentiated by their capability of forming smaller aggregates (with no extended surfaces) by either themselves or else in combination with each other and/or characterized by their relatively high solubility in [the] suitable liquid medium. Paragraph [0002]. US 2004/0105881 specifically discloses that "incorporation of a surfactant into a bilayer membrane that is built from another less soluble amphiphat, such as a phospholipid, can increase the flexibility of the resulting complex membrane . . . promot[ing] the capability of complex aggregates . . . to cross pores in a semi-permeable membrane that otherwise would prevent comparably large aggregates from crossing." Paragraph [0015]. Citation of any reference in this section of the application is not an admission that the reference is prior art to the application. The above noted publications are hereby incorporated by reference in their entirety.

3. SUMMARY OF THE INVENTION

[0006] The invention encompasses vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective for the delivery of fatty acids and/or phospholipids in the treatment of disorders related to fatty acid metabolic disorders, including essential fatty acid deficiency. In a particular embodiment, the vesicular formulations comprise about 25% to about 30% surfactant by weight based on the total weight of the vesicular formulation. These vesicular formulations are suitable for any method of administration, *e.g.*, subcutaneously, topically, or intravenously.

[0007] In accordance with the present invention, the vesicular formulations of the invention are formulated to deliver fatty acids and phosphatidyl derivatives of fatty acids, such as arachidonic acid or omega-3 or omega-6 fatty acids. In accordance with this embodiment the vesicular formulations may optionally be formulated to include other lipids described herein, such as phosphatidyl choline, and surfactants. In accordance with the present invention, the vesicular formulations of the invention deliver essential fatty acids,

such as omega-3 fatty acids, to decrease the levels of triglycerides. Vesicular formulations of the invention which deliver essential fatty acids, such as omega-3 fatty acids, may be useful in the treatment of fatty acid metabolic disorders, such as essential fatty acid deficiency and hypertriglyceridemia. In one embodiment, the vesicular formulations which deliver essential fatty acids comprise a phosphatidylcholine derivative of a fatty acid, *e.g.*, a phosphatidylcholine derivative of an omega-3 fatty acid. In various embodiments, the vesicular formulation is one of the formulations set forth in Example Formulations 1-129.

[0008] "Fatty acid metabolic disorder" means a defect in one of the enzymes involved in fatty acid metabolism, and include fatty oxidation disorders, whereby the body is unable to oxidize and metabolize fatty acids due to a failure in the enzymatic pathway. "Essential fatty acid deficiency" means a deficiency in the essential fatty acids, *e.g.*, omega-3 and omega-6 fatty acids, which can lead to physical symptoms such as hemorrhagic dermatitis skin atrophy, scaly dermatitis , dry skin , weakness , impaired vision , tingling sensations , mood swings, edema , high blood pressure , high triglycerides , hemorrhagic folliculitis , hematologic disturbances , immune and mental deficiencies , and impaired growth.

[0009] In accordance with the present invention, the vesicular formulations of the invention deliver fats and fat soluble vitamins, such as vitamin E, for the treatment of disorders related to hypolididemia, including, abetalipoproteinemia, hypobetalipoproteinemia, chlyomicron retention disease. In one embodiment, the vesicular formulations which deliver fats and fat soluble vitamins comprise a phosphatidylcholine derivative of a fatty acid, *e.g.*, a phosphatidylcholine derivative of vitamin E. In various embodiments, the vesicular formulation is one of the formulations set forth in Example Formulations 1-129.

[0010] The invention encompasses vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering organic matter once delivered to the subject. These vesicular formulations are suitable for any method of administration, *e.g.*, subcutaneously, topically, or intravenously. Without in any way being limited by theory, it is believed that the surprisingly effective and capacious sequestration of native organic compounds by the vesicular formulations disclosed herein occurs because of liquid crystallinity of the vesicular formulations mediated by the presence of membrane adapters such as surfactants. In various embodiments, the vesicular formulation is one of the formulations set forth in Example Formulations 1-129. In a preferred embodiments, the vesicular formulations comprise about 25% to about 30% surfactant by weight.

[0011] In one embodiment, the invention encompasses vesicular formulations of lipids and surfactants capable of sequestering native organic compounds, including arachidonic acid, upon delivery to human skin for the treatment of pain or inflammation. In some embodiments, these formulations are designed such that the vesicles are able to penetrate deep tissue without diversion into the blood vessels. That is, the formulations are able to travel to the site of the pain in sufficient amount to alleviate that pain to some extent. In accordance with the invention, delivery to the deep tissue includes delivery of the formulation beneath the skin to the muscle tissue and to the joint itself, while limiting systemic delivery and exposure to the formulation. In a particular embodiment, the vesicular formulation is capable of sequestering arachidonic acid upon administration to human skin, and therefore is capable of altering the pathology of, *e.g.*, pain or inflammation. In another embodiment of the invention, vesicular formulations designed to sequester arachidonic acid may also be used to prevent the formation of metabolites, including eicosanoids, for the prevention and/or treatment of asthma, seborrheic eczema, bronchospasm, atherothrombatic cardiovascular disorders, venous thrombatic disorders, pain, and dysmenorrhea. In various embodiments, the vesicular formulation capable of sequestering arachidonic acid is one of the formulations set forth in Example Formulations 1-129.

[0012] In an embodiment of the invention, vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants can sequester cholesterol upon administration to human skin, thus decreasing the accumulation of or uptake of cholesterol for the treatment of hypercholesterolemia. The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering triglycerides, thus decreasing the accumulation or uptake of triglycerides for the treatment of hypertriglyceridemia. In various embodiments, the vesicular formulation capable of sequestering cholesterol or triglycerides is one of the formulations set forth in Example Formulations 1-129.

[0013] The vesicular formulations of the invention may also be used to sequester factors involved in fatty acid metabolism, such as hormone sensitive lipase (HSL). Inhibition of HSL inhibits the conversion of triglycerides to glycerol and fatty acids, resulting in a decrease in plasma free fatty acids. Thus, the vesicular formulations of the invention have utility where the decrease in plasma fatty acids is desired, including insulin resistance, metabolic syndrome X, dyslipidemias and abnormal lipoprotein metabolism. In various embodiments, the vesicular formulation capable of sequestering factors involved in fatty acid metabolism is one of the formulations set forth in Example Formulations 1-129.

[0014] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering metal (as a chelator) upon administration to human skin for the treatment of, *e.g.*, metal toxicity. In various embodiments, the vesicular formulation capable of sequestering metals is one of the formulations set forth in Example Formulations 1-129.

[0015] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering a toxin (*e.g.*, DDT) upon administration to human skin. In various embodiments, the vesicular formulation capable of sequestering toxins such as DDT is one of the formulations set forth in Example Formulations 1-129.

[0016] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering inflammatory mediators (*e.g.*, cytokines, such as interleukins, or presenting antigens) upon administration to human skin for the treatment of inflammation and inflammatory related disorders, such as asthma. In various embodiments, the vesicular formulation capable of sequestering inflammatory mediators is one of the formulations set forth in Example Formulations 1-129.

[0017] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering amyloid upon administration for the treatment of Alzheimer's disease. Such formulations may be administered intravenously in accordance with this embodiment. In various embodiments, the vesicular formulation capable of sequestering amyloid is one of the formulations set forth in Example Formulations 1-129.

[0018] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering uric acid upon administration for the treatment of gout or macular degeneration, such as AMD. Such formulations may be administered topically or intravitreally in accordance with this embodiment. In various embodiments, the vesicular formulation capable of sequestering uric acid is one of the formulations set forth in Example Formulations 1-129.

[0019] The invention relates to vesicular formulations comprising one or more phospholipids and one or more nonionic surfactants that are effective in sequestering squalene, thus leading to fungistatic activity against, *e.g.*, hyphal fungi. These vesicular formulations are suitable for any method of administration, *e.g.*, subcutaneously, topically, or

intravenously. In various embodiments, the vesicular formulation capable of sequestering squalene is one of the formulations set forth in Example Formulations 1-129.

[0020] The formulations of the invention are formulated in the absence of any pharmaceutically active agent, *i.e.*, any non-lipid non-surfactant pharmaceutically active agent.

[0021] As used herein, the term "formulation" is not meant to imply that the ingredients or components are in combination with a pharmaceutically active agent, *i.e.*, any non-lipid non-surfactant active agent that has received regulatory approval for the treatment of fatty acid related disorders, hypocholesterolemia, hypertriclyceridemia, pain, including osteoarthritic pain, inflammation, infection, or toxicity, including metal toxicity or any of the disorders listed above.

[0022] Despite the lack of a recognized active agent, the vesicles elicit a therapeutic effect, namely the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or any of the disorders listed above. Without being bound by any theory, Applicant believes that the vesicle components themselves are responsible for this effect.

[0023] In one embodiment, the invention provides a pharmaceutical package or kit comprising one or more containers filled with the formulation of the invention, and instructions for administration of the formulation to a patient or subject in need thereof for the treatment of any disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or any of the disorders listed above. In certain embodiments, the formulation comprises one or more phospholipids and one or more surfactants. In certain embodiments, the formulation does not comprise a pharmaceutically active agent, *i.e.*, any non-lipid, non-surfactant pharmaceutically active agent that has received marketing or regulatory approval in any country for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia, hypercholesterolemia, pain, including osteoarthritic pain, inflammation, infection, including fungal or bacterial infection, or toxicity, including metal toxicity, or any of the other disorders listed above. In various embodiments, the container comprises a formulation formulated as a suspension, emulsion, gel, cream, lotion, spray, film forming solution or lacquer. The invention provides packages or kits that can be used in any of the above-described methods.

[0024] In one embodiment, the invention comprises a method for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia,

hypercholesterolemia, or any of the disorders listed above, wherein the vesicular formulations of the invention are administered over a period of one or more weeks, for example for at least five weeks, six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, or twelve weeks, sixteen weeks, twenty four weeks, four months, six months, eight months, ten months, one year, two or more years, or indefinitely.

[0025] In one embodiment, the formulations of the invention comprise one or more phospholipids, one or more nonionic surfactants, in the absence of any pharmaceutically active agent, *i.e.*, any non-lipid non-surfactant pharmaceutically active agent that has received regulatory approval for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia, hypercholesterolemia pain, including osteoarthritic pain, inflammation, infection, including fungal or bacterial infection, or toxicity, including metal toxicity, or any of the disorders listed above.

[0026] In one embodiment, a 0.1 to 10 gram dose of the formulation of the invention is administered to the patient for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or any of the disorders listed above; a 1 to 10 gram dose of the formulation is administered to the patient for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia, hypercholesterolemia, or any of the disorders listed above; a 1 to 5 gram dose of the formulation is administered to the patient for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia, hypercholesterolemia, pain, including osteoarthritic pain, inflammation, infection, including fungal or bacterial infection, or toxicity, including metal toxicity, or any of the disorders listed above; or a 1 gram, 2 gram, 3 gram, 4 gram, 5 gram, 6 gram, 7 gram, 8 gram, 9 gram or 10 gram dose of the formulation is administered to the patient for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia, hypercholesterolemia pain, including osteoarthritic pain, inflammation, infection, including fungal or bacterial infection, or toxicity, including metal toxicity, or any of the disorders listed above. In some embodiments, the dose is measured as the total weight of the deformasome. In some embodiments, the dose is measured as the total weight of the lipid(s) and surfactant(s) in the deformasome. The dose may be administered once or twice daily for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or any of the disorders listed above. The dose may be administered once, twice, three, four, five, six, or seven times per week in

accordance with the invention. The dose may be administered every day, every other day, or two to three times a week in accordance with the invention.

[0027] In some embodiments, the lipid in the pharmaceutical composition is a phospholipid. In some embodiments, the second lipid is a lysophospholipid. In some embodiments, the surfactant is a non-ionic surfactant.

[0028] In some embodiments, the compositions of the invention form vesicles or other extended surface aggregates (ESAs), wherein the vesicular preparations have improved permeation capability through the semi-permeable barriers, such as skin. The adaptability and deformability of the vesicles allow the vesicles to penetrate beneath the skin to the muscle and the joint itself, however, the size of the vesicle prevents penetration into the vasculature and as a result prevents systemic delivery. While not to be limited to any mechanism of action, the formulations of the invention are able to form vesicles characterized by their deformability and/or adaptability. The adaptability or deformability of the vesicles may be determined by the ability of the vesicles to penetrate a barrier with pores having an average pore diameter at least 50% smaller than the average vesicle diameter before the penetration.

[0029] In some embodiments, the vesicular compositions of the invention provide for targeted delivery of *e.g.*, fatty acids to phospholipase-rich sites, *e.g.*, tissues that are part of an inflammatory process or sites containing microorganisms such as bacteria (including narcadia) or fungi. While not to be limited to any mechanism of action or by any theory, the vesicular compositions of the invention are broken down by phospholipases. Thus, phospholipases that are released as part of the inflammatory process (*e.g.*, cancer or asthma) or that are released upon contact with a microorganism such as bacteria or fungi can lead to a number of effects including but not limited to rapid entry of the vesicular compositions into the target tissue, changes in the intracellular or intramembraneous lipid homeostasis, which may lead to increased apoptosis or altered membrane function, including increased permeability, and rapid metabolism of the vesicular composition with release of its constituents.

4. DETAILED DESCRIPTION OF THE INVENTION

[0030] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific

terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0031] The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, sheep, goat, pig, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

[0032] As used herein, a "sufficient amount," "amount effective to" or an "amount sufficient to" achieve a particular result refers to an amount of the formulation of the invention is effective to produce a desired effect, which is optionally a therapeutic effect (*i.e.*, by administration of a therapeutically effective amount). Alternatively stated, a "therapeutically effective" amount is an amount that provides some alleviation, mitigation, and/or decrease in at least one clinical symptom. Clinical symptoms associated with the disorder that can be treated by the methods of the invention are well-known to those skilled in the art. Further, those skilled in the art will appreciate that the therapeutic effects need not be complete or curative, as long as some benefit is provided to the subject. For example, a "sufficient amount" or "an amount sufficient to" can be an amount that is effective to treat the symptoms of fatty acid deficiencies, hypertriglyceridemia or hypercholesterolemia or other joint or muscle pain.

[0033] As used herein, the terms "treat", "treating" or "treatment of" mean that the severity of a subject's condition is reduced or at least partially improved or ameliorated and/or that some alleviation, mitigation or decrease in at least one clinical symptom is achieved and/or there is an inhibition or delay in the progression of the condition and/or delay in the progression of the onset of disease or illness. The terms "treat", "treating" or "treatment of" also means managing the disease state.

[0034] As used herein, the term "pharmaceutically acceptable" when used in reference to the formulations of the invention denotes that a formulation does not result in an unacceptable level of irritation in the subject to whom the formulation is administered. Preferably such level will be sufficiently low to provide a formulation suitable for approval by regulatory authorities.

[0035] As used herein with respect to numerical values, the term "about" means a range surrounding a particular numeral value which includes that which would be expected to result from normal experimental error in making a measurement. For example, in certain embodiments, the term "about" when used in connection with a particular numerical value

means ±20%, unless specifically stated to be ±1%, ±2%, ±3%, ±4%, ±5%, ±10%, ±15%, or ±20% of the numerical value.

[0036] The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkyl may optionally be substituted with one or more substituents Q as described herein. The term "alkyl" also encompasses both linear and branched alkyl, unless otherwise specified. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 12 (C_{1-12}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or a branched saturated monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 12 (C_{3-12}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms), n-propyl, isopropyl, butyl (including all isomeric forms), n-butyl, isobutyl, sec-butyl, t-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms). For example, C_{1-6} alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. It is understood in the chemical arts, that the use of the longer chains described herein may be appropriate, or appropriate only in limited amounts, within a molecule so that the properties of the resulting molecule (such as solubility) are appropriate for the use. Thus, while those in the art may use the above longer length alkyl substituents they will be used only when appropriate to provide the desired function.

[0037] The term "aryl" refers to a monocyclic aromatic group and/or multicyclic monovalent aromatic group that contain at least one aromatic hydrocarbon ring. In certain embodiments, the aryl has from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to bicyclic or tricyclic carbon rings, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). In certain embodiments, aryl may also be optionally substituted with one or more substituents Q as described herein.

[0038] The term "heteroaryl" refers to a monocyclic aromatic group and/or multicyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, and N. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N

atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. The heteroaryl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl. Examples of bicyclic heteroaryl groups include, but are not limited to, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, isobenzofuranyl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, dihydroisoindolyl, and tetrahydroquinolinyl. Examples of tricyclic heteroaryl groups include, but are not limited to, carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, and xanthenyl. In certain embodiments, heteroaryl may also be optionally substituted with one or more substituents Z as described herein.

[0039] The term "alkenoyl" as used herein refers to –C(O)-alkenyl. The term "alkenyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, carbon-carbon double bonds. The alkenyl may be optionally substituted with one or more substituents Z as described herein. The term "alkenyl" also embraces radicals having "*cis*" and "*trans*" configurations, or alternatively, "Z" and "E" configurations, as appreciated by those of ordinary skill in the art. As used herein, the term "alkenyl" encompasses both linear and branched alkenyl, unless otherwise specified. For example, C_{2-6} alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 30 (C_{2-30}), 2 to 24 (C_{2-24}), 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 12 (C_{2-12}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 30 (C_{3-30}), 3 to 24 (C_{3-24}), 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 12 (C_{3-12}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propen-1-yl, propen-2-yl, allyl, butenyl, and 4-methylbutenyl. In certain embodiments, the alkenoyl is mono-alkenoyl, which contains one carbon-carbon double bond. In certain embodiments, the alkenoyl is di-alkenoyl, which contains two carbon-carbon double bonds. In certain

embodiments, the alkenoyl is poly-alkenoyl, which contains more than two carbon-carbon double bonds.

[0040] The term "heterocyclyl" or "heterocyclic" refers to a monocyclic non-aromatic ring system and/or multicyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, or N; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, acridinyl, azepinyl, benzimidazolyl, benzindolyl, benzoisoxazolyl, benzisoxazinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzofuranyl, benzonaphthofuranyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiadiazolyl, benzothiazolyl, benzothiophenyl, benzotriazolyl, benzothiopyranyl, benzoxazinyl, benzoxazolyl, benzothiazolyl, β-carbolinyl, carbazolyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dibenzofuranyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydropyranyl, dioxolanyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrazolyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, furanyl, imidazolidinyl, imidazolinyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indazolyl, indolinyl, indolizinyl, indolyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroindolyl, octahydroisoindolyl, oxadiazolyl, oxazolidinonyl, oxazolidinyl, oxazolopyridinyl, oxazolyl, oxiranyl, perimidinyl, phenanthridinyl, phenathrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, 4-piperidonyl, pteridinyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridopyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuryl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydropyranyl, tetrahydrothienyl, tetrazolyl,

thiadiazolopyrimidinyl, thiadiazolyl, thiamorpholinyl, thiazolidinyl, thiazolyl, thienyl, triazinyl, triazolyl, and 1,3,5-trithianyl. In certain embodiments, heterocyclic may also be optionally substituted with one or more substituents Z as described herein.

[0041] The term "halogen", "halide" or "halo" refers to fluorine, chlorine, bromine, and/or iodine.

[0042] The term "optionally substituted" is intended to mean that a group, including alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl, may be substituted with one or more substituents Z, in one embodiment, one, two, three or four substituents Z, where each Z is independently selected from the group consisting of cyano, halo, oxo, nitro, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-14} aralkyl, heteroaryl, heterocyclyl, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)NR^fR^g$, $-C(NR^e)NR^fR^g$, $-OR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)NR^fR^g$, $-OC(=NR^e)NR^fR^g$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)NR^fR^g$, $-OS(O)_2NR^fR^g$, $-NR^fR^g$, $-NR^eC(O)R^f$, $-NR^eC(O)OR^f$, $-NR^eC(O)NR^fR^g$, $-NR^eC(=NR^h)NR^fR^g$, $-NR^eS(O)R^f$, $-NR^eS(O)_2R^f$, $-NR^eS(O)NR^fR^g$, $-NR^eS(O)_2NR^fR^g$, $-SR^e$, $-S(O)R^e$, $-S(O)_2R^e$, and $-S(O)_2NR^fR^g$, wherein each R^e, R^f, R^g, and R^h is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-14} aralkyl, heteroaryl, or heterocyclyl; or R^f and R^g together with the N atom to which they are attached form heterocyclyl.

[0043] The term "solvate" refers to a compound provided herein or a salt thereof, which further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0044] In accordance with this disclosure, the term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term "consisting of" excludes any element, step, or ingredient not specified; and the term "consisting essentially of" excludes any element, step, or ingredient that materially changes a basic characteristic of the invention.

[0045] In some embodiments, the formulation of the invention provided herein comprise at least one lipid, preferably a phospholipid, at least one surfactant, preferably a nonionic surfactant, optionally suspended in a pharmaceutically acceptable medium, preferably an aqueous solution, preferably having a pH ranging from 3.5 to 9.0, preferably from 4 to 7.5. The formulation of the invention may optionally contain buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and/or thickeners. In some embodiments, the formulation of the invention comprises a mixture of more than one lipid,

preferably more than one phospholipids. In some embodiments, the formulation of the invention consists essentially of at least one lipid, preferably a phospholipid, at least one surfactant, preferably a nonionic surfactant, a pharmaceutically acceptable carrier, and optionally buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and/or thickeners. In some embodiments, the formulation of the invention consists of at least one lipid, preferably a phospholipid, at least one surfactant, preferably a nonionic surfactant, a pharmaceutically acceptable carrier, and one or more of the following: buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and thickeners.

4.1. LIPID

[0046] In the sense of this disclosure, a "lipid" is any substance, which has properties like or similar to those of a fat. As a rule, it has an extended apolar group (the "chain", X) and generally also a water-soluble, polar hydrophilic part, the "head" group (Y) and has the basic Formula I:

$$X—Y_n \textbf{(I)}$$

wherein n is equal to or larger than zero.

[0047] Lipids with n=0 are referred to as apolar lipids and lipids with n≥1 are referred to as polar lipids. In this sense, all amphiphilic substances, including, but not limited to glycerides, glycerophospholipids, glycerophosphinolipids, glycerophosphonolipids, sulfolipids, sphingolipids, isoprenoid lipids, steroids or sterols and carbohydrate-containing lipids can generally be referred to as lipids, and are included as such in this disclosure. A list of relevant lipids and lipid related definitions is provided in EP 0 475 160 A1 (*see, e.g.* p. 4, l. 8 to p. 6, l. 3) and U.S. Patent No. 6,165,500 (*see, e.g.*, col. 6, l. 10 to col. 7, l. 58), each incorporated herein by reference in their entirety.

[0048] A phospholipid in various embodiments may contain (1) a moiety derived from glycerol or a sphingosine, (2) a phosphate group, and/or (3) simple organic molecule such as choline. A phospholipid as used herein may, for example, be a compound of Formula II:

$$R^1—CH_2—CHR^2—CR^3H—O—PHO_2—O—R^4 \textbf{(II)}$$

wherein R^1 and R^2 are hydrogen, OH, an alkyl group, an aliphatic chain, an aliphatic chain derived from a fatty acid or a fatty alcohol; provided however that R^1 and R^2 cannot both be hydrogen, OH or a C_1-C_3 alkyl group.; In some embodiments R^1 and R^2 are independently, an

aliphatic chain, most often derived from a fatty acid or a fatty alcohol; R^3 generally is a hydrogen.

[0049] The OH-group of the phosphate is a hydroxyl radical or hydroxyl anion (*i.e.*, hydroxide) form, dependent on degree of the group ionization. Furthermore, R^4 may be a proton or a short-chain alkyl group, substituted by a tri-short-chain alkylammonium group, such as a trimethylammonium group, or an amino-substituted short-chain alkyl group, such as 2-trimethylammonium ethyl group (cholinyl) or 2-dimethylammonium short alkyl group.

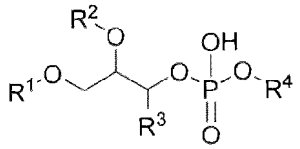
[0050] A sphingophospholipid is, for example, a compound of Formula IIB:

$$R^1\text{—Sphingosine—O—}PHO_2\text{—O—}R^4 \textbf{(IIB)}$$

wherein R^1 is a fatty-acid attached via an amide bond to the nitrogen of the sphingosine and R^4 has the meanings given under Formula II.

[0051] A lipid preferably is a substance of formulae II or IIB, wherein R^1 and/or R^2 are acyl or alkyl, n-hydroxyacyl or n-hydroxyalkyl, but may also be branched, with one or more methyl groups attached at almost any point of the chain; usually, the methyl group is near the end of the chain (iso or anteiso). The radicals R^1 and R^2 may moreover either be saturated or unsaturated (mono-, di- or poly-unsaturated). R^3 is hydrogen and R^4 is 2-trimethylammonium ethyl (the latter corresponds to the phosphatidyl choline head group), 2-dimethylammonium ethyl, 2-methylammonium ethyl or 2-aminoethyl (corresponding to the phosphatidyl ethanolamine head group). R^4 may also be a proton (giving phosphatidic acid), a serine (giving phosphatidylserine), a glycerol (giving phosphatidylglycerol), an inositol (giving phosphatidylinositol), or an alkylamine group (giving phosphatidylethanolamine in case of an ethylamine), if one chooses to use a naturally occurring glycerophospholipid. Otherwise, any other sufficiently polar phosphate ester, such that will form a lipid bilayer, may be considered as well for making the formulations of the disclosure.

[0052] A phospholipid is, for example, a compound of Formula IIC:



(IIC)

wherein R^1 and R^2 are independently an acyl group, alkyl group, n-hydroxyacyl group, or n-hydroxyalkyl group, most often derived from a fatty acid or a fatty alcohol, wherein R^1 and R^2 may also be branched, with one or more methyl groups attached at almost any point of the

chain; usually, the methyl group is near the end of the chain (iso or anteiso), wherein R^1 and R^2 cannot both be hydrogen, OH or a C_1-C_3 alkyl group. The radicals R^1 and R^2 may moreover either be saturated or unsaturated (mono-, di- or poly-unsaturated). R^3 generally is a hydrogen. The OH-group of the phosphate is a hydroxyl radical or hydroxyl anion (*i.e.*, hydroxide) form, dependent on degree of the group ionization. Furthermore, R^4 may be a proton or a short-chain alkyl group, substituted by a tri-short-chain alkylammonium group, such as a trimethylammonium group, or an amino-substituted short-chain alkyl group, such as 2-trimethylammonium ethyl group (cholinyl) or 2-dimethylammonium short alkyl group. R^4 may be 2-trimethylammonium ethyl (the latter corresponds to the phosphatidyl choline head group), 2-dimethylammonium ethyl, 2-methylammonium ethyl or 2-aminoethyl (corresponding to the phosphatidyl ethanolamine head group). R^4 may also be a proton (giving phosphatidic acid), a serine (giving phosphatidylserine), a glycerol (giving phosphatidylglycerol), an inositol (giving phosphatidylinositol), or an alkylamine group (giving phosphatidylethanolamine in case of an ethylamine), if one chooses to use a naturally occurring glycerophospholipid. Otherwise, any other sufficiently polar phosphate ester, such that will form a lipid bilayer, may be considered as well for making the formulations of the disclosure.

Table 1 lists preferred phospholipids in accordance with one embodiment of the disclosure.

Table 1

Preferred (phospho)lipids

Fatty chain		Phospholipid: Type and Charge					
Name(s)	Length: nr. of double bonds	Phosphatidylcholine / ±	Phosphatidylethanolamine / ±	Sphingomyelin / +	Phosphatidylglycerol / -	Phosphatidylinositol / -	Phosphatidic acid / -
		Main lipid, L1	Main lipid, L1	Main lipid, L1	Aux. lipid, L2	Aux. lipid, L2	Aux. lipid, L2
	C24						
Behen(o)yl	C22						
Eruca(o)yl	C22:1-13cis						
Arachin(o)yl	C20						
Gadolen(o)yl	C20:1-11cis						
Arachidon(o)yl	C20:4-5,8,11,14cis						
Ole(o)yl	C18:1-9cis	DOPC	DOPE	SM-oleyl	DOPG	DOPI	DOPA
Stear(o)yl	C18						
Linol(o)yl	C18:2-9,12cis	(Soy-PC /	(Soy-PE /	Brain SM	(Soy-PC /	(Soy-PI /	(Soy-PA /
Linole(n/o)yl	C18:3-9,12,15cis	Egg-PC)	Egg-PE)		Egg-PC)	Liver-PI)	Egg-PA)
Palmitole(o)yl	C18:1-9cis						
Palmit(o)yl	C16						
Myrist(o)yl	C14	DMPC	DMPE	SM-myristyl	DMPG	DMPI	
Laur(o)yl	C12	DLPC	DLPE	SM-lauryl			DLPA
Capr(o)yl	C10						
Rel. concentration range L1/L2 (M/M)			**1/0**	**1/0**	**10/1-1/1**	**10/1-3/1**	**10/1-5/1**
"Total Lipid"* concentration range (w-%)			**0.5-45**	**0.5-45**	**0.5-40**	**0.5-40**	**0.5-40**

**Total Lipid includes phospholipid(s), surfactant(s)t and all lipophilic excipients*

[0053] The preferred lipids in the context of this disclosure are uncharged and form stable, well hydrated bilayers; phosphatidylcholines, phosphatidylethanolamine, and sphingomyelins are the most prominent representatives of such lipids. Any of those can have chains as listed in the Table 1, the ones forming fluid phase bilayers, in which lipid chains are in disordered state, being preferred.

[0054] Different negatively charged, *i.e.*, anionic, lipids can also be incorporated into vesicular lipid bilayers. Attractive examples of such charged lipids are phosphatidylglycerols, phosphatidylinositols and, somewhat less preferred, phosphatidic acid (and its alkyl ester) or phosphatidylserine. It will be realized by anyone skilled in the art that it is less commendable to make vesicles just from the charged lipids than to use them in a combination with electro-neutral bilayer component(s). In case of using charged lipids, buffer composition and/or pH care must selected so as to ensure the desired degree of lipid head-group ionization and/or the desired degree of electrostatic interaction between the, oppositely, charged drug and lipid molecules. Moreover, as with neutral lipids, the charged bilayer lipid components can in principle have any of the chains listed in the Table 1. The chains forming fluid phase lipid bilayers are clearly preferred, however, both due to vesicle adaptability increasing role of increasing fatty chain fluidity and due to better ability of lipids in fluid phase to mix with each other.

[0055] The fatty acid- or fatty alcohol-derived chain of a lipid is typically selected amongst the basic aliphatic chain types given in the following tables:

Table 2: The (most) preferred basic, straight, saturated fatty chain residues

Shorthand designation	Systematic name	Trivial name
12:0	Dodecanoic	Lauric
13:0	Tridecanoic	
14:0	Tetradecanoic	Myristic
15:0	Pentadecanoic	
16:0	Hexadecanoic	Palmitic
17:0	Heptadecanoic	Margaric
18:0	Octadecanoic	Stearic
19:0	Nonadecanoic	
20:0	Eicosanoic	Arachidic
21:0	Heneicosanoic	
22:0	Docosanoic	Behenic
23:0	Tricosanoic	
24:0	Tetracosanoic	Lignoceric

Table 3: The (most) preferred monoenoic fatty chain residues

Shorthand designation	Systematic name	Trivial name
9-14:1 / 14:1(n-5)	cis-9-Tetradecenoic	Myristoleic
7-16:1 / 16:1(n-9)	cis-7-Hexadecenoic	
9-16:1 / 16:1(n-7)	cis-9-Hexadecenoic	Palmitoleic
9-18:1 / 18:1(n-9)	cis-9-Octadecenoic	Oleic
11-18:1 / 18:1(n-7)	cis-11-Octadecenoic	cis-Vaccenic
11-20:1 / 20:1(n-9)	cis-11-Eicosenoic	Gondoic
14-20:1 / 20:1(n-6)	cis-14-Eicosaenoic	
13-22:1 / 22:1(n-9)	cis-13-Docosenoic	Erucic
15-24:1 / 24:1(n-9)	cis-15-Tetracosenoic	Nervoni
3t-18:1	trans-3-Hexadecenoi	
9t-18:1	trans-9-Octadecenoic	Elaidic
11t-18:1	trans-11-Octadecenoic	Vaccenic

Table 4: The (most) preferred dienoic and polyenoic fatty chain residues

Shorthand designation	Systematic name	Trivial name
10,13c-16:2 / 16:2(n-3)	10-cis,13-cis-Hexadecadienoic	
7,10c-16:2 / 16:3(n-6)	7-cis,10-cis -Hexadecadienoic	
7,10,13c-16:3 / 16:3(n-3)	7-cis,10-cis,13-cis-Hexadecatrienoic	
12,15c-18:2 / 18:2(n-3)	12-cis,15-cis-Octadecadienoic	α-Linoleic
10,12t-18:2 / 18:2(n-6)	trans-10,trans-12-Octadecadienoic	
9,12c-18:2 / 18:2(n-6)	9-cis,12-cis-Octadecadienoic	γ-Linoleic
9,12,15c-18:3 / 18:3(n-3)	9-cis,12-cis,15-cis-Octadecatrienoic	α-Linolenic
6,9,12c-18:3 / 18:3(n-6)	6-cis,9-cis,12-cis-Octadecatrienoic	γ-Linolenic
9c,11c,13t-18:3	9-cis,11-trans,13-trans-Octadecatrienoic	α-Eleostearic
8t,10t,12c-18:3	8-trans,10-trans,12-cis-Octadecatrienoic	Calendic
6,9,12,15c-18:4 / 18:4(n-3)	6,9,12,15-Octadecatetraenoic	Stearidonic
3,6,9,12c-18:4 / 18:4(n-6)	3,6,9,12-Octadecatetraenoic	
3,6,9,12,15c-18:5 / 18:5(n-3)	3,6,9,12,15-Octadecapentaenoic	
14,17c-20:2 / 20:2(n-3)	14-cis,17-cis-Eicosadienoic	
11,14c-20:2 / 20:2(n-6)	11-cis,14-cis-Eicosadienoic	
11,14,17c-20:3 / 20:3(n-3)	8-cis,11-cis,14-cis-Eicosatrienoic	Dihomo-α-linolenic
8,11,14c-20:3 / 20:3(n-6)	8-cis,11-cis,14-cis-Eicosatrienoic	Dihomo-γ-linolenic
5,8,11c-20:3 20:3(n-9)	5,8,11all-cis-Eicosatrienoic	'Mead's'
5,8,11,14c-20:4 / 20:4(n-6)	5,8,11;14-all-cis-Eicosatetraenoic	Arachidonic
8,11,14,17c-20:4 / 20:4(n-3)	8,11,14,17-all-cis-Eicosatetraenoic	
5,8,11,14,17c-20:5 or 20:5(n-3)	5,8,11,14,17-all-cis-Eicosapentaenoic	
13,16c-22:2	13,16-Docosadienoic	
13,16,19c-22:3 / 22:3(n-3)	13,16,19-Docosatrienoic	
10,13,16c-22:3 / 22:3(n-6)	10,13,16-Docosatrienoic	
7,10,13,16c-22:4 / 22:4(n-6)	7,10,13,16-Docosatetraenoic	Adrenic
4,7,10,13,16c-22:5 or 22:5(n-6)	4,7,10,13,16-Docosapentaenoic	
4,7,10,13,16,19c-22:5 or 22:6(n-3)	4,7,10,13,16,19-Docosahexaenoic	

[0056] Other double bond combinations or positions are possible as well.

[0057] Suitable fatty residues can furthermore be branched, for example, can contain a methyl group in an iso or anteiso position of the fatty acid chain, or else closer to the chain middle, as in 10-*R*-methyloctadecanoic acid or tuberculostearic chain. Relatively important

amongst branched fatty acids are also isoprenoids, many of which are derived from 3,7,11,15-tetramethylhexadec-trans-2-en-1-ol, the aliphatic alcohol moiety of chlorophyll. Examples include 5,9,13,17-tetramethyloctadecanoic acid and especially 3,7,11,15-tetramethylhexadecanoic (phytanic) and 2,6,10,14-tetramethylpentadecanoic (pristanic) acids. A good source of 4,8,12-trimethyltridecanoic acid are marine organisms. Combination of double bonds and side chains on a fatty residue are also possible.

[0058] Alternatively, suitable fatty residues may carry one or a few oxy- or cyclic groups, especially in the middle or towards the end of a chain. The most prominent amongst the later, alicyclic fatty acids, are those comprising a cyclopropane (and sometimes cyclopropene) ring, but cyclohexyl and cycloheptyl rings can also be found and might be useful for purposes of this disclosure. 2-(D)-Hydroxy fatty acids are more ubiquitous than alicyclic fatty acids, and are also important constituents of sphingolipids. Also interesting are 15-hydroxy-hexadecanoic and 17-hydroxy-octadecanoic acids, and maybe 9-hydroxy-octadeca-*trans*-10,*trans*-12-dienoic (dimorphecolic) and 13-hydroxy-octadeca-*cis*-9,*trans*-11-dienoic (coriolic) acid. Arguably the most prominent hydroxyl-fatty acid in current pharmaceutical use is ricinoleic acid, (D-(-)12-hydroxy-octadec-*cis*-9-enoic acid, which comprises up to 90% of castor oil, which is also often used in hydrogenated form. Epoxy-, methoxy-, and furanoid-fatty acids are of only limited practical interest in the context of this disclosure.

[0059] Generally speaking, unsaturation, branching or any other kind of derivatization of a fatty acid is best compatible with the intention of present disclosure of the site of such modification is in the middle or terminal part of a fatty acid chain. The *cis*-unsaturated fatty acids are also more preferable than *trans*-unsaturated fatty acids and the fatty radicals with fewer double bonds are preferred over those with multiple double bonds, due to oxidation sensitivity of the latter. Moreover, symmetric chain lipids are generally better suited than asymmetric chain lipids.

[0060] A preferred lipid of the Formula II is, for example, a natural phosphatidylcholine, which used to be called lecithin. It can be obtained from egg (rich in palmitic, $C_{16:0}$, and oleic, $C_{18:1}$, but also comprising stearic, $C_{18:0}$, palmitoleic, $C_{16:1}$, linolenic, $C_{18:2}$, and arachidonic, $C_{20:4}$, radicals), soybean (rich in unsaturated C_{18} chains, but also containing some palmitic radical, amongst a few others), coconut (rich in saturated chains), olives (rich in monounsaturated chains), saffron (safflower) and sunflowers (rich in n-6 linoleic acid), linseed (rich in n-3 linolenic acid), from whale fat (rich in monounsaturated n-3 chains), from primrose or primula (rich in n-3 chains). Preferred, natural phosphatidyl ethanolamines (used

to be called cephalins) frequently originate from egg or soybeans. Preferred sphingomyelins of biological origin are typically prepared from eggs or brain tissue. Preferred phosphatidylserines also typically originate from brain material whereas phosphatidylglycerol is preferentially extracted from bacteria, such as E. Coli, or else prepared by way of transphosphatidylation, using phospholipase D, starting with a natural phosphatidylcholine. The preferably used phosphatidylinositols are isolated from commercial soybean phospholipids or bovine liver extracts. The preferred phosphatidic acid is either extracted from any of the mentioned sources or prepared using phospholipase D from a suitable phosphatidylcholine.

[0061] Furthermore, synthetic phosphatidyl cholines (R^4 in Formula II corresponds to 2-trimethylammonium ethyl), and R^1 and R^2 are aliphatic chains, as defined in the preceding paragraph with 12 to 30 carbon atoms, preferentially with 14 to 22 carbon atoms, and even more preferred with 16 to 20 carbon atoms, under the proviso that the chains must be chosen so as to ensure that the resulting ESAs comprise fluid lipid bilayers. This typically means use of relatively short saturated and of relatively longer unsaturated chains. Synthetic sphingomyelins (R^4 in Formula IIB corresponds to 2-trimethylammonium ethyl), and R^1 is an aliphatic chain, as defined in the preceding paragraph, with 10 to 20 carbon atoms, preferentially with 10 to 14 carbon atoms per fully saturated chain and with 16-20 carbon atoms per unsaturated chain.

[0062] Synthetic phosphatidyl ethanolamines (R^4 is 2-aminoethyl), synthetic phosphatidic acids (R^4 is a proton) or its ester (R^4 corresponds, for example, to a short-chain alkyl, such as methyl or ethyl), synthetic phosphatidyl serines (R^4 is L- or D-serine), or synthetic phosphatidyl (poly)alcohols, such as phosphatidyl inositol, phosphatidyl glycerol (R^4 is L- or D-glycerol) are preferred as lipids, wherein R^1 and R^2 are fatty residues of identical or moderately different type and length, especially such as given in the corresponding tables given before in the text. Moreover, R^1 can represent alkenyl and R^2 identical hydroxyalkyl groups, such as tetradecylhydroxy or hexadecylhydroxy, for example, in ditetradecyl or dihexadecylphosphatidyl choline or ethanolamine, R^1 can represent alkenyl and R^2 hydroxyacyl, such as a plasmalogen (R^4 trimethylammonium ethyl), or R^1 can be acyl, such as lauryl, myristoyl or palmitoyl and R^2 can represent hydroxy as, for example, in natural or synthetic lysophosphatidyl cholines or lysophosphatidyl glycerols or lysophosphatidyl ethanolamines, such as 1-myristoyl or 1-palmitoyllysophosphatidyl choline or -phosphatidyl ethanolamine; frequently, R^3 represents hydrogen.

[0063] A lipid of Formula IIB is also a suitable lipid within the sense of this disclosure. In Formula IIB, n=1, R^1 is an alkenyl group, R^2 is an acylamido group, R^3 is hydrogen and R^4 represents 2-trimethylammonium ethyl (choline group). Such a lipid is known under the name of sphingomyelin.

[0064] Suitable lipids furthermore are a lysophosphatidyl choline analog, such as 1-lauroyl-1,3-dihydroxypropane-3-phosphoryl choline, a monoglyceride, such as monoolein or monomyristin, a cerebroside, ceramide polyhexoside, sulfatide, sphingoplasmalogen, a ganglioside or a glyceride, which does not contain a free or esterified phosphoryl or phosphono or phosphino group in the 3 position. An example of such a glyceride is diacylglyceride or 1-alkenyl-1-hydroxy-2-acyl glyceride with any acyl or alkenyl groups, wherein the 3-hydroxy group is etherified by one of the carbohydrate groups named, for example, by a galactosyl group such as a monogalactosyl glycerin.

[0065] Lipids with desirable head or chain group properties can also be formed by biochemical means, for example, by means of phospholipases (such as phospholipase A1, A2, B, C and, in particular, D), desaturases, elongases, acyl transferases, etc., from natural or synthetic precursors.

[0066] Furthermore, a suitable lipid is any lipid, which is contained in biological membranes and can be extracted with the help of apolar organic solvents, such as chloroform. Aside from the lipids already mentioned, such lipids also include, for example, steroids, such as estradiol, or sterols, such as cholesterol, beta-sitosterol, desmosterol, 7-keto-cholesterol or beta-cholestanol, fat-soluble vitamins, such as retinoids, vitamins, such as vitamin A1 or A2, vitamin E, vitamin K, such as vitamin K1 or K2 or vitamin D1 or D3, etc.

[0067] The less soluble amphiphilic components comprise or preferably comprise a synthetic lipid, such as myristoleoyl, palmitoleoyl, petroselinyl, petroselaidyl, oleoyl, elaidyl, cis- or trans-vaccenoyl, linolyl, linolenyl, linolaidyl, octadecatetraenoyl, gondoyl, eicosaenoyl, eicosadienoyl, eicosatrienoyl, arachidoyl, cis- or trans-docosaenoyl, docosadienoyl, docosatrienoyl, docosatetraenoyl, lauroyl, tridecanoyl, myristoyl, pentadecanoyl, palmitoyl, heptadecanoyl, stearoyl or nonadecanoyl, glycerophospholipid or corresponding derivatives with branched chains or a corresponding dialkyl or sphingosin derivative, glycolipid or other diacyl or dialkyl lipid.

[0068] The more soluble amphiphilic components(s) is/are frequently derived from the less soluble components listed above and, to increase the solubility, substituted and/or

complexed and/or associated with a butanoyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl or undecanoyl substituent or several, mutually independent, selected substituents or with a different material for improving the solubility.

[0069] A further suitable lipid is a diacyl- or dialkyl-glycerophosphoetha- nolamine azo polycthoxylene derivative, a didecanoylphosphatidyl choline or a diacylphosphoolligomaltobionamide.

[0070] In certain embodiments, the amount of lipid in the formulation is from about 1% to about 12%, about 1% to about 10%, about 1% to about 4%, about 4% to about 7% or about 7% to about 10% by weight. In a specific embodiment, the lipid is a phospholipid. In another specific embodiment, the phospholipid is a phosphatidylcholine.

[0071] In some embodiments, the lipid in the formulation does not comprise an alkyl-lysophospholipid. In some embodiments, the lipid in the formulation does not comprise a polyeneylphosphatidylcholine.

4.2. SURFACTANT

[0072] The term "surfactant" has its usual meaning. A list of relevant surfactants and surfactant related definitions is provided in EP 0 475 160 A1 (*see, e.g.,* p. 6, l. 5 to p.14. l.17)and U.S. Pat. No. 6,165,500 (*see, e.g.,* col. 7, l. 60 to col. 19, l. 64), each herein incorporated by reference in their entirety, and in appropriate surfactant or pharmaceutical Handbooks, such as Handbook of Industrial Surfactants or US Pharmacopoeia, Pharm. Eu. In some embodiments, the surfactants are those described in Tables 1-18 of U.S. Patent Application Publication No. 2002/0012680 A1, published January 31, 2002, the disclosure of which is herein incorporated by reference in its entirety. The following list therefore only offers a selection, which is by no means complete or exclusive, of several surfactant classes that are particularly common or useful in conjunction with present patent application. Preferred surfactants to be used in accordance with the disclosure include those with an HLB greater than 12. The list includes ionized long-chain fatty acids or long chain fatty alcohols, long chain fatty ammonium salts, such as alkyl- or alkenoyl-trimethyl-, -dimethyl- and -methyl-ammonium salts, alkyl- or alkenoyl-sulphate salts, long fatty chain dimethyl-aminoxides, such as alkyl- or alkenoyl-dimethyl-aminoxides, long fatty chain, for example alkanoyl, dimethyl-aminoxides and especially dodecyl dimethyl-aminoxide, long fatty chain, for example alkyl-N-methylglucamide- s and alkanoyl-N-methylglucamides, such as MEGA-

8, MEGA-9 and MEGA-10, N-long fatty chain-N,N-dimethylglycines, for example N-alkyl-N,N-dimethylglycines, 3-(long fatty chain-dimethylammonio)-alkane- sulphonates, for example 3-(acyidimethylammonio)-alkanesulphonates, long fatty chain derivatives of sulphosuccinate salts, such as bis(2-ethylalkyl) sulphosuccinate salts, long fatty chain-sulphobetaines, for example acyl-sulphobetaines, long fatty chain betaines, such as EMPIGEN BB or ZWITTERGENT-3-16, -3-14, -3-12, -3-10, or -3-8, or polyethylen-glycol-acylphenyl ethers, especially nonaethylen-glycol-octyl- phenyl ether, polyethylene-long fatty chain-ethers, especially polyethylene-acyl ethers, such as nonaethylen-decyl ether, nonaethylen-dodecyl ether or octaethylene-dodecyl ether, polyethyleneglycol-isoacyl ethers, such as octaethyleneglycol-isotridecyl ether, polyethyleneglycol-sorbitane-long fatty chain esters, for example polyethyleneglycol-sorbitane-acyl esters and especially polyoxyethylene-monolaurate (*e.g.* polysorbate 20 or Tween 20), polyoxyethylene-sorbitan-monooleate (*e.g.* polysorbate 80 or Tween 80), polyoxyethylene-sorbitan-monolauroleylate, polyoxyethylene -sorbitan-monopetroselinate, polyoxyethylene -sorbitan-- monoelaidate, polyoxyethylene -sorbitan-myristoleylate, polyoxyethylene -sorbitan-palmitoleinylate, polyoxyethylene-sorbitan-p- etroselinylate, polyhydroxyethylene-long fatty chain ethers, for example polyhydroxyethylene-acyl ethers, such as polyhydroxyethylene-lauryl ethers, polyhydroxyethylene-myristoyl ethers, polyhydroxyethylene-cetylst- earyl, polyhyd roxyethylene-palmityl ethers, polyhyd roxyethylene-oleoyl ethers, polyhydroxyethylene-palmitoleoyl ethers, polyhydroxyethylene-lino- leyl, polyhydroxyethylen-4, or 6, or 8, or 10, or 12-lauryl, miristoyl, palmitoyl, palmitoleyl, oleoyl or linoeyl ethers (Brij series), or in the corresponding esters, polyhydroxyethylen-laurate, -myristate, -palmitate, -stearate or -oleate, especially polyhydroxyethylen-8-stearate (Myrj 45) and polyhydroxyethylen-8-oleate, polyethoxylated castor oil 40 (Cremophor EL), sorbitane-mono long fatty chain, for example alkylate (Arlacel or Span series), especially as sorbitane-monolaurate (Arlacel 20, Span 20), long fatty chain, for example acyl-N-methylglucamides, alkanoyl-N-methylglucamides, especially decanoyl-N-methylglucamide, dodecanoyl-N-methylglucamide, long fatty chain sulphates, for example alkyl-sulphates, alkyl sulphate salts, such as lauryl-sulphate (SDS), oleoyl-sulphate; long fatty chain thioglucosides, such as alkylthioglucosides and especially heptyl-, octyl- and nonyl-beta-D-thioglucopyranoside; long fatty chain derivatives of various carbohydrates, such as pentoses, hexoses and disaccharides, especially alkyl-glucosides and maltosides, such as hexyl-, heptyl-, octyl-, nonyl- and decyl-beta-D-glucopyranoside or D-maltopyranoside; further a salt, especially a sodium salt, of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurodeoxycholate, taurocholate, a fatty acid salt, especially

oleate, elaidate, linoleate, laurate, or myristate, most often in sodium form, lysophospholipids, n-octadecylene-glycerophosphatidic acid, octadecylene-phosphorylglycerol, octadecylene-phosphorylserine, n-long fatty chain-glycero-phosphatidic acids, such as n-acyl-glycero-phosphatidic acids, especially lauryl glycero-phosphatidic acids, oleoyl-glycero-phosphatidic acid, n-long fatty chain-phosphorylglycerol, such as n-acyl-phosphorylglycerol, especially lauryl-, myristoyl-, oleoyl- or palmitoeloyl-phosphorylglycerol, n-long fatty chain-phosphorylserine, such as n-acyl-phosphorylserine, especially lauryl-, myristoyl-, oleoyl- or palmitoeloyl-phosphorylserine, n-tetradecyl-glycero-phosphatidic acid, n-tetradecyl-phosphorylglycerol, n-tetradecyl-phosphorylserine, corresponding-, elaidoyl-, vaccenyl-lysophospholipids, corresponding short-chain phospholipids, as well as all surface active and thus membrane destabilising polypeptides. Surfactant chains are typically chosen to be in a fluid state or at least to be compatible with the maintenance of fluid-chain state in carrier aggregates.

[0073] Table 5 lists preferred surfactants in accordance with one embodiment of the disclosure.

Table 5

Preferred surfactants

Fatty chain		Nonionic surfactants (S) Head / Type / TM				
Name(s)	Length: nr. of double bonds	POE-sorbitan-ester	POE-ether	POE-ester	POE-phenoxy-ether	
		Tween	*Brij, Macrogol*	*Myrj, Nonex*	*Triton*	*Selected brandnames*
	C24					
Behen(o)yl	C22					
Eruca(o)yl	C22:1-13cis					
Arachin(o)yl	C20					
Gadolen(o)yl	C20:1-11cis					
Arachidon(o)yl	C20:4-5,8,11,14cis					
Ole(o)yl	C18:1-9cis	**Tween 80**	**Brij 98**	**Simulsol-2599**	**TritonX100****	
Stear(o)yl	C18	**Tween 60**		**Myrj-52**		
Linol(o)yl	C18:2-9,12cis					
Linole(n/o)yl	C18:3-9,12,15cis					
Palmitole(o)yl	C18:1-9cis					
Palmit(o)yl	C16	**Tween 40**		NN		
Myrist(o)yl	C14					
Laur(o)yl	C12	**Tween 20**	**Brij 35**	NN		
Capr(o)yl	C10					
Rel. concentration range L/S (M/M)		**5/1 - 1/1**	**5/1 - 1/1**	**5/1 - 1/1**	**4/1 - 3/2**	

NN: not
readily
available in
the market
but in principle
suitable

**Triton is not an oleate, but an octylphenoxy-POE
derivative
Myrj-45: Stearoyl-EO8; Myrj-49: Stearoyl-EO20 (not in the market); Myrj-59:
Stearoyl-EO100; Myrj-52: Stearoyl-EO40;
Simulsol-2599 = Macrogol-10-oleate

Brij-98: Oleoyl-EO20
Brij-35: Lauryl-EO23

[0074] In certain embodiments, the surfactant is a nonionic surfactant. The surfactant may be present in the formulation in about 1% to about 10%, about 1% to about 4%, about 4% to about 7% or about 7% to about 10% by weight. In some embodiments, the amount of surfactants in the formulation is from about 0.2% to about 0.5%. In certain embodiments, the nonionic surfactant is selected from the group consisting of: polyoxyethylene sorbitans (polysobate surfactants), polyhydroxyethylene stearates or polyhydroxyethylene laurylethers (Brij surfactants). In a specific embodiment, the surfactant is a polyoxyethylene-sorbitan-monooleate (*e.g.* polysorbate 80 or Tween 80). In certain embodiments, the polysorbate can have any chain with 12 to 20 carbon atoms. In certain embodiments, the polysorbate is fluid in the formulation, which may contain one or more double bonds, branching, or cyclo-groups.

4.3. FORMULATIONS

[0075] In some embodiments, the formulations of the invention comprise only one lipid and only one surfactant. In other embodiments, the formulations of the invention comprise more than one lipid and only one surfactant, *e.g.*, two, three, four, or more lipids and one surfactant. In other embodiments, the formulations of the invention comprise only one lipid and more than one surfactant, *e.g.*, two, three, four, or more surfactants and one lipid. In other embodiments, the formulations of the invention comprise more than one lipid and more than one surfactant, *e.g.*, two, three, four, or more lipids and two, three, four, or more surfactants.

[0076] The formulations of the invention may have a range of lipid to surfactant ratios. The ratios may be expressed in terms of molar terms (mol lipid /mol surfactant). The molar ratio of lipid to surfactant in the formulations may be from about 1:3 to about 30:1, from about 1:2 to about 30:1, from about 1:1 to about 30:1, from about 5:1 to about 30:1, from about 10:1 to about 30:1, from about 15:1 to about 30:1, or from about 20:1 to about 30:1. In certain embodiments, the molar ratio of lipid to surfactant in the formulations of the invention may be from about 1:2 to about 10:1. In certain embodiments, the ratio is from about 1:1 to about 2:1, from about 2:1 to about 3:1, from about 3:1 to about 4:1, from about 4:1 to about 5:1 or from about 5:1 to about 10:1. In certain embodiments, the molar ratio is from about 10.1 to about 30:1, from about 10:1 to about 20:1, from about 10:1 to about 25:1, and from about 20:1 to about 25:1. In specific embodiments, the lipid to surfactant ratio is about 1.0:1.0, about 1.25:1.0, about 1.5/1.0, about 1.75/1.0, about 2.0/1.0, about 2.5/1.0, about 3.0/1.0 or about 4.0/1.0.

[0077] The formulations of the invention may also have varying amounts of total amount of the following components: lipid and surfactant combined (TA). The TA amount may be stated in terms of weight percent of the total composition. In one embodiment, the TA is from about 1% to about 40%, about 5% to about 30%, about 7.5% to about 15%, about 5% to about 10%, about 10% to about 20% or about 20% to about 30%. In specific embodiments, the TA is 8%, 9%, 10%, 15% or 20%.

[0078] Selected ranges for total lipid amounts and lipid/surfactant ratios (mol/mol) for the formulations of the invention are described in Table 6 below:

Table 6: Total Amount and Lipid to Surfactant Ratios

TA (and surfactant) (%)	Lipid/Surfactant (mol/mol)
5 to 10	1.0 to 1.25
5 to 10	1.25 to 1.75
5 to 10	1.75 to 2.25
5 to 10	2.25 to 3.00
5 to 10	3.00 to 4.00
5 to 10	4.00 to 8.00
5 to 10	10.00 to 13.00
5 to 10	15.00 to 20.00
5 to 10	20.00 to 22.00
5 to 10	22.00 to 25.00
10 to 20	1.0 to 1.25
10 to 20	1.25 to 1.75
10 to 20	1.25 to 1.75
10 to 20	2.25 to 3.00
10 to 20	3.00 to 4.00
10 to 20	4.00 to 8.00
10 to 20	10.00 to 13.00
10 to 20	15.00 to 20.00
10 to 20	20.00 to 22.00
10 to 20	22.00 to 25.00

[0079] The formulations of the invention do not comprise a pharmaceutically active agent that has received marketing or regulatory approval in any country for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or any other disorder listed above.

[0080] The formulations of the invention may optionally contain one or more of the following ingredients: co-solvents, chelators, buffers, antioxidants, preservatives, microbicides, emollients, humectants, lubricants and thickeners. Preferred amounts of optional components are described in Table 7.

[0081] The formulations of the invention may include a buffer to adjust the pH of the aqueous solution to a range from pH 3.5 to pH 9, pH 4 to pH 7.5, or pH 4 to pH 6.5. Examples of buffers include, but are not limited to, acetate buffers, lactate buffers, phosphate buffers, and propionate buffers.

[0082] The formulations of the invention are typically formulated in aqueous media. The formulations may be formulated with or without co-solvents, such as lower alcohols

[0083] A "microbicide" or "antimicrobial" agent is commonly added to reduce the bacterial count in pharmaceutical formulations. Some examples of microbicides are short chain alcohols, including ethyl and isopropyl alcohol, chlorbutanol, benzyl alcohol, chlorbenzyl alcohol, dichlorbenzylalcohol, hexachlorophene; phenolic compounds, such as cresol, 4-chloro-m-cresol, p-chloro-m-xylenol, dichlorophene, hexachlorophene, povidon-iodine; parabenes, especially alkyl-parabenes, such as methyl-, ethyl-, propyl-, or butyl-paraben, benzyl paraben; acids, such as sorbic acid, benzoic acid and their salts; quaternary ammonium compounds, such as alkonium salts, *e.g.*, a bromide, benzalkonium salts, such as a chloride or a bromide, cetrimonium salts, *e.g.*, a bromide, phenoalkecinium salts, such as phenododecinium bromide, cetylpyridinium chloride and other salts; furthermore, mercurial compounds, such as phenylmercuric acetate, borate, or nitrate, thiomersal, chlorhexidine or its gluconate, or any antibiotically active compounds of biological origin, or any suitable mixture thereof..

[0084] Examples of "antioxidants" are butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT) and di-tert-butylphenol (LY178002, LY256548, HWA-131, BF-389, CI-986, PD-127443, E-5119, BI-L-239XX, etc.), tertiary butylhydroquinone (TBHQ), propyl gallate (PG), 1-O-hexyl-2,3,5-trimethylhydroquinone (HTHQ); aromatic amines (diphenylamine, p-alkylthio-o-anisidine, ethylenediamine derivatives, carbazol, tetrahydroindenoindol); phenols and phenolic acids (guaiacol, hydroquinone, vanillin, gallic acids and their esters, protocatechuic acid, quinic acid, syringic acid, ellagic acid, salicylic acid, nordihydroguaiaretic acid (NDGA), eugenol); tocopherols (including tocopherols (alpha, beta, gamma, delta) and their derivatives, such as tocopheryl-acylate (*e.g.*, -acetate, -laurate, myristate, -palmitate, -oleate, -linolcate, etc., or an y other suitable tocopheryl-lipoate), tocopheryl-POE-succinate; trolox and corresponding amide and thiocarboxamide analogues; ascorbic acid and its salts, isoascorbate, (2 or 3 or 6)-o-alkylascorbic acids, ascorbyl esters (*e.g.*, 6-o-lauroyl, myristoyl, palmitoyl-, oleoyl, or linoleoyl-L-ascorbic acid, etc.). Also useful are the preferentially oxidised compounds, such as sodium bisulphite, sodium metabisulphite, thiourea; chellating agents, such as EDTA, GDTA, desferral;

miscellaneous endogenous defence systems, such as transferrin, lactoferrin, ferritin, cearuloplasmin, haptoglobion, heamopexin, albumin, glucose, ubiquinol-10); enzymatic antioxidants, such as superoxide dismutase and metal complexes with a similar activity, including catalase, glutathione peroxidase, and less complex molecules, such as beta-carotene, bilirubin, uric acid; flavonoids (flavones, flavonols, flavonones, flavanonals, chacones, anthocyanins), N-acetylcystein, mesna, glutathione, thiohistidine derivatives, triazoles; tannines, cinnamic acid, hydroxycinnamatic acids and their esters (coumaric acids and esters, caffeic acid and their esters, ferulic acid, (iso-) chlorogenic acid, sinapic acid); spice extracts (*e.g.,* from clove, cinnamon, sage, rosemary, mace, oregano, allspice, nutmeg); carnosic acid, carnosol, carsolic acid; rosmarinic acid, rosmaridiphenol, gentisic acid, ferulic acid; oat flour extracts, such as avenanthramide 1 and 2; thioethers, dithioethers, sulphoxides, tetralkylthiuram disulphides; phytic acid, steroid derivatives (*e.g.,* U74006F); tryptophan metabolites (*e.g.,* 3-hydroxykynurenine, 3-hydroxyanthranilic acid), and organochalcogenides.

[0085] "Thickeners" are used to increase the viscosity of pharmaceutical formulations to and may be selected from selected from pharmaceutically acceptable hydrophilic polymers, such as partially etherified cellulose derivatives, comprising carboxymethyl-, hydroxyethyl-, hydroxypropyl-, hydroxypropylmethyl- or methyl-cellulose; completely synthetic hydrophilic polymers comprising polyacrylates, polymethacrylates, poly(hydroxyethyl)-, poly(hydroxypropyl)-, poly(hydroxypropylmethyl)methacrylate, polyacrylonitrile, methallyl-sulphonate, polyethylenes, polyoxiethylenes, polyethylene glycols, polyethylene glycol-lactide, polyethylene glycol-diacrylate, polyvinylpyrrolidone, polyvinyl alcohols, poly(propylmethacrylamide), poly(propylene fumarate-co-ethylene glycol), poloxamers, polyaspartamide, (hydrazine cross-linked) hyaluronic acid, silicone; natural gums comprising alginates, carrageenan, guar-gum, gelatine, tragacanth, (amidated) pectin, xanthan, chitosan collagen, agarose; mixtures and further derivatives or co-polymers thereof and/or other pharmaceutically, or at least biologically, acceptable polymers.

[0086] The formulations of the present invention may also comprise a polar liquid medium. The formulations of the invention may be administered in an aqueous medium. The of the present invention may be in the form of a solution, suspension, emulsion, cream, lotion, ointment, gel, spray, film forming solution or lacquer.

[0087] In some embodiments, the invention relates to the use of a vesicular formulation as described above for the preparation of a pharmaceutical composition for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and

hypercholesterolemia. In some embodiments, the invention relates to a vesicular formulation or pharmaceutical composition comprising at least one phospholipid and one nonionic surfactant for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia wherein the formulation or pharmaceutical composition is formulated for subcutaneous, topical or intravenous delivery.

[0088] Table 7 lists preferred excipients for the formulation.

Table 7

Preferred excipients for use in the formulations of the invention

Designated activity						
Antioxidant	Molar (M) or Rel. w%*	**Antibiotic**	Molar (M) or Weight-%	**Buffer**	Molar
Primary					
Butylated hydroxyanisole, BHA	0.1-8	**Acetate**	30-150 mM		30-150 mM
Butylated hydroxytoluene, BHT	0.1-4	**Benzyl alcohol**	0.1-3	**Acetate**	
Thymol	0.1-1	**Butylparabene**	0.1-3	**Phosphate**	10-50 mM
Metabisulphite (MW = 190.1)	1-5 mM	**Ethylparabene**	0.1-3		30-150
Bisulphite	1-5 mM	**Imidurea** (MW = 368.30)	0.1-1	Triethanolamine HCL	mM
Thiourea (MW = 76.12)	1-10 mM	**Dimethoxane** (MW = 174.2)	0.03-0.1		
Monothioglycerol (MW = 108.16)	1-20 mM	**Methylparabene**	0.1-5		
Propyl gallate (MW = 212.2)	0.02-0.2	**Phenoxyethanol**	0.1-5		
Ascorbate (MW = 175.3+ ion)	1-10 mM	Benzalkonium chloride	0.01-0.2		
Palmityl-ascorbate	0.01-1	Benzethonium chloride	0.01-0.1		
Tocopherol PEG	0.5-5	Phenol	0.05-2		
Secondary (chelator)		Phenylethyl alcohol	0.1-1		
EDTA (MW = 292)	1-10 mM	Thimerosal	0.005-0.1		
EGTA (MW = 380.35)	1-10 mM				
Desferal (MW = 656.79)	0.1-5 mM				

**As percentage of Total Lipid quantity*

EGTA= Ethylene glycol-bis-(2-aminoethyl)-N,N,N', N'-tetraacetic acid

EDTA = Ethylenedioxy-diethylene-dinitrilo-tetraacetic acid

4.4. VESICULAR FORMULATIONS

[0089] While not to be limited to any mechanism of action or any theory, the formulations of the invention may form vesicles or ESAs characterized by their adaptability, deformability, or penetrability.

[0090] The term vesicle or aggregate "adaptability" which governs the "tolerable surface curvature" is defined as the ability of a given vesicle or aggregate to change easily its properties, such as shape, elongation ratio, and surface to volume ratio. The vesicles of this invention may be characterized by their ability to adjust the aggregates' shape and properties to the anisotropic stress caused by pore crossing. Sufficient adaptability implies that a vesicle or an aggregate can sustain different unidirectional forces or stress, such as one caused by pressure, without extensive fragmentation, which defines a "stable" aggregate. If an aggregate passes through a barrier fulfilling this condition the terms "adaptability" and (shape) "deformability" plus "permeability" are essentially equivalent. A "barrier" in the context of this invention is (as in, for example, EP 0 475 160 and WO 98/17255) a body with through-extending narrow pores, such narrow pores having a radius which is at least 25% smaller than the radius of the ESAs (considered as spherical) before said ESAs permeate through such pores.

[0091] The term "narrow" used in connection with a pore implies that the pore radius is significantly, typically at least 25%, smaller than the radius of the entity tested with regard to its ability to cross the pore. The necessary difference typically should be greater for the narrower pores. Using 25% limit is therefore quite suitable for >150 nm diameter whereas >100% difference requirement is more appropriate for the smaller systems, *e.g.*, with <50 nm diameter. For diameters around 20 nm, aggregate diameter difference of at least 200% is often required.

[0092] The term "semipermeable" used in connection with a barrier implies that a solution can cross transbarrier openings whereas a suspension of non-adaptable aggregates (large enough for the above definition of "narrow" pores to apply) cannot. Conventional lipid vesicles (liposomes) made from any common phosphatidylcholine in the gel lamellar phase or else from any biological phosphatidylcholine/cholesterol 1/1 mol/mol mixture or else comparably large oil droplets, all having the specified relative diameter, are three examples for such non-adaptable aggregates.

[0093] The term "stable" means that the tested aggregates do not change their diameter spontaneously or under the transport related mechanical stress (*e.g.* during passage through a semipermeable barrier) unacceptably, which most often means only to a pharmaceutically acceptable degree. A 20-40% change is normally considered acceptable; the halving or doubling of aggregate diameter is borderline and a greater change in diameter is typically unacceptable. Alternatively and very conveniently, the change in aggregate diameter resulting from pore crossing under pressure is used to assess system stability; the same criteria are then applied as for "narrow" pores, mutatis mutandis. To obtain the correct value for aggregate diameter change, a correction for flux/vortex effects may be necessary. These procedures are described in greater detail in the publications of the applicant in Cevc *et. al.*, Biochim. Biophys. Acta 2002; 1564:21-30.

[0094] Non-destructing passage of ultradeformable, mixed lipid aggregates through narrow pores in a semi-permeable barrier is thus diagnostic of high aggregate adaptability. If pore radius is two times smaller than the average aggregate radius the aggregate must change its shape and surface-to-volume ratio at least 100% to pass without fragmentation through the barrier. An easy and reversible change in aggregate shape inevitably implies high aggregate deformability and requires large surface-to-volume ratio adaptation. A change in surface-to-volume ratio per se implies: a) high volume compressibility, *e.g.* in the case of compact droplets containing material other than, and immiscible with, the suspending fluid; b) high aggregate membrane permeability, *e.g.* in the case of vesicles that are free to exchange fluid between inner and outer vesicle volume.

[0095] The vesicles or ESAs of the present invention have "adaptability" that can be assessed using the following method: 1) measure the flux (j_a) of the aggregate or ESA suspension through a semi-permeable membrane (*e.g.*, gravimetrically) for different transport-driving trans barrier pressures (Δp); 2) calculate the pressure dependence of barrier penetratability P for the suspension by dividing each measured flux value by the corresponding pressure value: $P(\Delta p) = j_a(\Delta p)/\Delta p$; 3) monitor the ratio of final and starting vesicle diameter $2\,r_{ves}(\Delta p)/2\,r_{ves,0}$ (*e.g.* by dynamic light scattering), wherein $2\,r_{ves}(\Delta p)$ is the vesicle diameter after semi-permeable barrier passage driven by Δp and $2\,r_{ves,0}$ is the starting vesicle diameter, and if necessary make corrections for the flow-effects; and 4) align both data sets $P(\Delta p)$ vs. $r_{ves}(\Delta p)/r_{ves,0}$ to determine the co-existence range for high aggregate adaptability and stability.

[0096] It is also useful, but not essential, to parameterize experimental penetratability data within the framework of Maxwell-approximation in terms of the necessary pressure value p* and in terms of maximum penetratability value P_{max}. It is plausible to sum-up all the contributions to a moving aggregate energy (deformation energy/ies, thermal energy, the shearing work, etc.) into a single, total energy. The equilibrium population density of aggregate's energetic levels then may be taken to correspond to Maxwell's distribution. All aggregates with a total energy greater than the activation energy, $E_f E_A$, are finally concluded to penetrate the barrier. The pore-crossing probability for such aggregates is then given by the following formula, where *e* is dimensionless aggregate energy units of the activation energy E_A:

$$P(e) = 1 - erf\left(\sqrt{\frac{1}{e}}\right) + \sqrt{\frac{4}{\pi e}} \cdot \exp\left[-\frac{1}{e}\right]$$

[0097] It is therefore plausible to represent barrier penetrability of a given suspension as a function of transport driving pressure by the following formula, where P_{max} is the maximum possible penetratability of a given barrier (for the aggregates with zero transport resistance this penetrability is identical to the penetrability of the suspending medium flux), and p* is an adjustable parameter that describes the pressure sensitivity, and thus the transport resistance, of the tested system (for barriers with a fixed pore radius this sensitivity is a function of aggregate properties solely; for non-interacting particles the sensitivity is dominated by aggregate adaptability, allowing to make the assumption: a_a proportional to 1/p*

$$P(p) = p_{\max} \cdot \left\{1 - erf\left(\sqrt{\frac{p^*}{p}}\right) + \sqrt{\frac{4p^*}{\pi p}} \cdot \exp\left[-\frac{p^*}{p}\right]\right\}$$

[0098] Other methods of testing deformability and adaptability which may be used to characterize the compositions of the invention are set forth, for example, in U.S. Patent Application Publication Nos. 2004/0071767 and 2004/0105881, each herein incorporated by reference as if set forth herein in their entirety.

4.5. METHODS OF ADMINISTRATION / TREATMENT

[0099] In another embodiment, the invention provides methods of treating disorders related to fatty acid deficiencies, fatty acid metabolism, hypolididemia, hypertriglyceridemia and hypercholesterolemia comprising administering to a subject in need thereof a pharmaceutical composition comprising at least one phospholipid and one nonionic surfactant. In another embodiment, the invention provides methods of treating disorders related to fatty acid deficiencies, fatty acid metabolism, hypolididemia, hypertriglyceridemia and hypercholesterolemia comprising administering to a subject in need thereof a pharmaceutical composition consisting essentially of at least one phospholipid and one nonionic surfactant, a pharmaceutically acceptable carrier, and optionally buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and/or thickeners. In another embodiment, the invention provides methods of treating disorders related to fatty acid deficiencies, fatty acid metabolism, hypolididemia, hypertriglyceridemia and hypercholesterolemia comprising administering to a subject in need thereof a pharmaceutical composition consisting of at least one phospholipid and one nonionic surfactant, a pharmaceutically acceptable carrier, and one or more of the following: buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and thickeners.

[00100] In another embodiment, the invention provides methods of treating disorders related to inflammation, asthma, bronchospasm, atherothrombatic cardiovascular disorders, venous thrombatic disorders, pain, dysmenorrheal, hypercholesterolemia, hypertriglyceridemia, fatty acid metabolism, metal or other toxicity, Alzheimer's disease, gout or macular degeneration, such as AMD, or fungal infection, comprising administering to a subject in need thereof a pharmaceutical composition comprising at least one phospholipid and one nonionic surfactant, wherein the pharmaceutical composition sequesters organic matter upon administration. In another embodiment, the invention provides methods of treating disorders related to inflammation, asthma, bronchospasm, atherothrombatic cardiovascular disorders, venous thrombatic disorders, pain, dysmenorrheal, hypercholesterolemia, hypertriglyceridemia, fatty acid metabolism, metal or other toxicity, Alzheimer's disease, gout or macular degeneration, such as AMD, or fungal infection comprising administering to a subject in need thereof a pharmaceutical composition consisting essentially of at least one phospholipid and one nonionic surfactant, a pharmaceutically acceptable carrier, and optionally buffers, antioxidants, preservatives,

microbicides, antimicrobials, emollients, co-solvents, and/or thickeners, wherein the pharmaceutical composition sequesters organic matter upon administration. In another embodiment, the invention provides methods of treating disorders related to inflammation, asthma, bronchospasm, atherothrombatic cardiovascular disorders, venous thrombatic disorders, pain, dysmenorrheal, hypercholesterolemia, hypertriglyceridemia, fatty acid metabolism, metal or other toxicity, Alzheimer's disease, gout or macular degeneration, such as AMD, or fungal infection comprising administering to a subject in need thereof a pharmaceutical composition consisting of at least one phospholipid and one nonionic surfactant, a pharmaceutically acceptable carrier, and one or more of the following: buffers, antioxidants, preservatives, microbicides, antimicrobials, emollients, co-solvents, and thickeners, wherein the pharmaceutical composition sequesters organic matter upon administration.

4.6. PACKAGES

[0100] In another embodiment, the invention provides a pharmaceutical package or kit comprising one or more containers filled with the formulation of the invention, and instructions for administration of the formulation to a patient or subject in need thereof for treating disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia . In certain embodiments, the formulation comprises one or more phospholipids and one or more surfactants. In certain embodiments, the formulation does not comprise a non-lipid non-surfactant pharmaceutically active agent that has received marketing or regulatory approval in any country for the treatment of disorders related to fatty acid deficiencies, fatty acid metabolism, hypertriglyceridemia and hypercholesterolemia, or other disorder listed above . In various embodiments, the container comprises a formulation formulated as a suspension, emulsion, gel, cream, lotion, spray, film forming solution or lacquer. The invention provides packages or kits that can be used in any of the above-described methods.

5. EXAMPLES

5.1 Example 1: Example Formulations

[0101] The following exemplary formulations for topical application may be prepared by the following procedure:

1. Organic phase production, which contains all lipophilic excipients

The organic phase is produced by weighing the lipid, the surfactant, any additional lipophilic excipients into suitable containers followed by mixing these components into anoptically isotropic phase which appears as a clear solution. During mixing, the organic phase will be heated up, but temperature must not rise above 45 °C.

2. Aqueous phase production

The aqueous phase is prepared by weighing the non-lipophilic components and water, which serves as solvent, into suitable containers and then mixing these components into a clear solution. During mixing, the temperature will be elevated to 40 °C.

3. Production of a concentrated intermediate by combination of both phases

The isotropic organic phase and the clear aqueous phase are combined under stirring in a suitable vessel. Before and during the combination the temperature of both phases must be kept between 35 °C and 45 °C. The resulting intermediate is homogenised mechanically at 40 °C. Before starting homogenisation, the pressure in the production vessel is lowered to – 0.08 MPa. The desired average carrier size is typically reached after 10 minutes of homogenisation.

Three process parameters must be controlled carefully during the production of the concentrated intermediate: temperature, homogeniser circulation velocity, and overall processing time.

4. Production of the final bulk product by mixing the concentrated intermediate with dilution buffer.

The concentrated intermediate is diluted with the dilution buffer to the intended final concentration. The mixture is carefully stirred in the mixing vessel at 20 °C to homogeneity.

[0102] Table 8 describes the amounts of surfactant and lipids, and other excipients in the transfersomes formulations, described in terms of the percent of the total amount of formulation.

TABLE 8: Preferred Formulations

Table 8A: This table lists the relative amounts of each of the components of Preferred Formulations

	Lipid mg/g	Surfactant mg/g (1 to 10% by wt.)	Buffer (pH 4-7.5)	Antimicrobials (0-10 mg/g)	Antioxidants (0-10mg/g)	Emollient (0-50 mg/g)	Other (0-50mg/g)	Chelator (0-25mg/g)
1	47.944	42.056	4	5.000	0.700	30.000	30.000	3.000
2	53.750	31.250	4	5.000	0.700	30.000	15.000	3.000
3	90.561	79.439	4	5.000	0.700	30.000	30.000	3.000
4	47.944	42.056	5	5.000	0.700	30.000	30.000	3.000
5	50.607	44.393	5	5.000	0.700	0.000	10.000	3.000
6	90.561	79.439	5	5.000	0.700	30.000	30.000	3.000
7	49.276	43.224	6.5	5.000	0.700	30.000	30.000	3.000
8	53.750	31.250	6.5	5.000	0.200	30.000	0.000	3.000
9	90.561	79.439	6.5	5.000	0.200	30.000	20.000	3.000
10	41.351	48.649	4	5.000	0.200	30.000	30.000	3.000
11	47.882	37.118	4	5.000	0.200	0.000	30.000	3.000
12	95.764	74.236	4	5.000	0.200	30.000	30.000	3.000
13	65.676	24.324	5	5.000	0.200	0.000	25.000	3.000
14	62.027	22.973	5	5.000	0.200	0.000	30.000	3.000
15	124.054	45.946	5	5.000	0.200	15.000	36.510	3.000
16	62.687	32.313	6.5	5.000	0.200	15.000	0.000	3.000
17	41.853	43.147	6.5	5.000	0.200	30.000	30.000	3.000
18	95.764	74.236	6.5	5.000	0.200	0.000	30.000	3.000
19	47.882	37.118	6.5	5.000	0.200	0.000	0.000	3.000
20	45.000	45.000	6.5	5.000	0.200	0.000	0.000	1.000
21	31.935	58.065	5	5.000	0.200	30.000	15.000	3.000
22	42.500	42.500	6.5	5.000	0.200	30.000	0.000	3.000
23	38.276	51.724	4	5.000	0.200	0.000	36.510	3.000
24	42.500	42.500	4	5.000	0.200	0.000	15.000	3.000
25	85.000	85.000	4	5.000	0.200	30.000	30.000	3.000
26	38.276	51.724	5	5.000	0.200	30.000	0.000	1.000
27	36.429	48.571	5	5.000	0.200	30.000	30.000	3.000
28	72.299	97.701	5	5.000	0.200	30.000	15.000	3.000

29	46.250	46.250	6.5	5.000	0.700	0.000	20.000	3.000
30	38.804	46.196	6.5	5.000	0.700	15.000	30.000	3.000
31	36.667	33.333	6.5	5.000	0.700	30.000	10.000	3.000
32	66.667	23.333	4	5.000	0.200	0.000	0.000	3.000
33	45.833	41.667	4	5.000	0.200	30.000	0.000	3.000
34	31.957	38.043	4	5.000	0.200	0.000	30.000	3.000
35	47.143	42.857	5	5.000	0.200	30.000	25.000	1.000
36	96.905	88.095	5	5.000	0.200	30.000	20.000	3.000
37	31.957	38.043	5	5.000	0.200	0.000	30.000	3.000
38	35.455	54.545	6.5	5.000	0.700	30.000	0.000	3.000
39	84.457	100.543	6.5	5.000	0.700	30.000	30.000	3.000
40	89.048	80.952	6.5	5.000	0.700	30.000	30.000	3.000
41	41.087	48.913	4	5.000	0.700	30.000	36.510	3.000
42	45.280	39.720	4	5.000	0.700	0.000	0.000	3.000
43	107.500	62.500	4	5.000	0.700	30.000	30.000	3.000
44	77.243	67.757	4	5.000	0.700	0.000	15.000	3.000
45	45.280	39.720	5	5.000	0.700	0.000	20.000	3.000
46	90.561	79.439	5	5.000	0.700	0.000	30.000	3.000
47	47.944	42.056	5	5.000	0.700	0.000	10.000	3.000
48	50.607	44.393	5.5	5.000	0.700	30.000	0.000	1.000
49	107.500	62.500	5.5	5.000	0.700	30.000	0.000	3.000
50	47.944	42.056	5.5	5.000	0.700	30.000	30.000	3.000
51	46.364	38.636	4	5.000	0.200	30.000	25.000	3.000
52	46.364	38.636	4	5.000	0.200	0.000	20.000	3.000
53	46.098	43.902	5	5.000	0.200	15.000	30.000	3.000
54	43.537	41.463	5	5.000	0.200	30.000	0.000	3.000
55	45.000	45.000	5	5.000	0.200	0.000	30.000	3.000
56	59.492	30.508	6.5	5.000	0.200	30.000	30.000	3.000
57	39.054	45.946	6.5	5.000	0.200	0.000	0.000	3.000
58	35.854	34.146	6.5	5.000	0.200	30.000	0.000	3.000
59	50.000	40.000	6.5	5.000	0.700	30.000	30.000	3.000
60	38.571	51.429	6.5	5.000	0.700	30.000	30.000	3.000
61	41.954	50.546	6.5	5.000	0.700	30.000	30.000	3.000
62	42.632	47.368	6.5	5.000	0.700	30.000	30.000	3.000
63	46.098	43.902	6.5	5.000	0.700	30.000	30.000	3.000

64	39.721	50.279	6.5	5.000	0.700	30.000	30.000	3.000
65	44.198	50.802	6.5	5.000	0.700	30.000	30.000	3.000
66	46.453	51.047	6.5	5.000	0.700	30.000	30.000	3.000
67	51.221	43.779	6.5	5.000	0.700	30.000	30.000	3.000
68	54.167	43.333	6.5	5.000	0.700	30.000	30.000	3.000
69	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
70	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
71	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
72	40.000	50.000	6.5	5.000	0.700	30.000	30.000	3.000
73	40.000	50.000	6.5	5.000	0.700	30.000	30.000	3.000
74	40.000	50.000	5.5	0.000	0.700	30.000	30.000	3.000
75	40.000	50.000	6.5	5.000	0.700	30.000	30.000	3.000
76	40.000	50.000	6.5	5.000	0.700	30.000	30.000	3.000
77	40.000	50.000	6.5	5.000	0.700	30.000	30.000	3.000
78	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
79	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
80	40.000	50.000	5.5	0.000	0.700	30.000	30.000	3.000
81	40.000	50.000	5.5	5.000	0.700	30.000	30.000	3.000
82	44.444	55.556	5.5	5.000	0.700	30.000	30.000	3.000
83	66.440	23.560	5.5	5.000	0.700	30.000	30.000	3.000
84	54.000	36.000	4	5.000	0.700	30.000	30.000	3.000
85	50.000	40.000	4	5.000	0.700	30.000	30.000	3.000
86	48.611	38.889	4	5.000	0.700	30.000	30.000	3.000
87	46.575	38.425	4	5.000	0.700	30.000	30.000	3.000
88	46.575	38.425	4	5.000	0.700	30.000	30.000	3.000
89	46.575	38.425	4	5.000	0.700	30.000	30.000	3.000
90	50.000	40.000	4.5	5.000	0.700	30.000	30.000	3.000
91	94.444	75.556	4	5.000	0.700	30.000	30.000	3.000
92	46.712	38.288	4	5.000	0.700	30.000	30.000	3.000
93	48.889	39.111	4	5.000	0.700	30.000	30.000	3.000
94	39.721	50.279	6.5	5.000	0.700	30.000	30.000	3.000
95	90.000	0.000	6.5	5.000	0.700	30.000	30.000	3.000
96	68.700	8.500	7.5	5.000	0.700	30.000	36.510	1.000
97	71.460	4.720	7.8	5.000	0.700	50.000	35.000	3.000
99	71.460	4.720	7.8	5.000	0.700	50.000	15.000	3.000

98	71.460	4.720	7.8	0.000	0.700	50.000	15.000	3.000
100	71.460	4.720	7.8	0.000	0.700	50.000	35.000	3.000
101	46.575	38.425	4	0.000	0.700	0.000	0.000	3.000
102	46.575	38.425	4	0.000	0.700	0.000	0.000	3.000
103	54.643	30.357	4	5.000	0.700	0.000	0.000	3.000
104	39.72	50.279	6.5	5.000	0.700	30.000	30.000	3.000
105	90.00		6.5	5.000	0.700	30.000	30.000	3.000
106	46.57	38.425	4		0.700			3.000
107	46.75	38.425	4		0.700			3.000
108	54.64	30.357	4		0.700			3.000
109	46.364	38.636	4	5.000	0.200	30.000	25.000	3.000
110	46.364	38.636	4	5.000	0.200	0.000	20.000	3.000
111	46.098	43.902	5	5.000	0.200	15.000	30.000	3.000
112	43.537	41.463	5	5.000	0.200	30.000	0.000	3.000
113	45.000	45.000	5	5.000	0.200	0.000	30.000	3.000
114	59.492	30.508	6.5	5.000	0.200	30.000	30.000	3.000
115	39.054	45.946	6.5	5.000	0.200	0.000	0.000	3.000
116	35.854	34.146	6.5	5.000	0.200	30.000	0.000	3.000
117	50.000	40.000	6.5	5.000	0.700	30.000	30.000	3.000
118	38.571	51.429	6.5	5.000	0.700	30.000	30.000	3.000
119	41.954	50.546	6.5	5.000	0.700	30.000	30.000	3.000
120	42.632	47.368	6.5	5.000	0.700	30.000	30.000	3.000
121	46.098	43.902	6.5	5.000	0.700	30.000	30.000	3.000
122	39.721	50.279	6.5	5.000	0.700	30.000	30.000	3.000
123	44.198	50.802	6.5	5.000	0.700	30.000	30.000	3.000
124	46.453	51.047	6.5	5.000	0.700	30.000	30.000	3.000
125	51.221	43.779	6.5	5.000	0.700	30.000	30.000	3.000
126	54.167	43.333	6.5	5.000	0.700	30.000	30.000	3.000
127	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
128	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000
129	66.440	23.560	6.5	5.000	0.700	30.000	30.000	3.000

Table 8B: The table lists the specific components of the formulas listed above.

Formula	Lipid	Surfactant	Buffer	Antimicrobial	Antioxidants	Emollient	Chelator	Other
1-4	Sphingomyelin, *e.g.*, brain	Tween 80	Lactate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
5-7	Sphingomyelin, lauroyl	Brij 98	Acetate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
8-12	Phosphatidyl choline + Phosphatidylglycerol	Brij 98	Phosphate	Benzyl alcohol or paraben	HTHQ	Glycerol	EDTA	Ethanol
13-16	Phosphatidyl choline + phosphatidylinositol	Span 20	Acetate	Benzyl alcohol or paraben	HTHQ	Glycerol	EDTA	Ethanol
17-18	Phosphatidyl choline + phosphatidic acid	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
19	Phosphatidyl choline + phosphatidic acid	Brij 98 + Tween 80	Phosphate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
20	Phosphatidyl choline + phosphatidic acid	Span 20 + Tween 80	Phosphate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
21	Phosphatidyl choline	Cremophor + Span 20	Lactate	Thimerosal	BHA	Glycerol	EDTA	Ethanol
22	Phosphatidyl	Cremophor	Lactate	Thimerosal	BHA	Glycerol	EDTA	Ethanol

	choline	+ Tween 80						
23-28	Phosphatidyl choline	Cremophor	Lactate	Thimerosal	BHA	Glycerol	EDTA	Ethanol
29-30	Phosphatidyl ethanolamine	Tween 80	Phosphate	Thimerosal	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
31	Phosphatidyl ethanolamine	Brij 98 + Tween 80	Phosphate	Thimerosal	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
32	Phosphatidyl glycerol	Cremophor + Brij 98	Acetate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
33-37	Phosphatidyl glycerol	Brij 98	Acetate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
38-40	Phosphatidyl ethanolamine	Cremophor	phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
41-47	Phosphatidyl glycerol	Tween 80	Propionate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
48-50	Phosphatidyl serine	Brij 98	Phosphate	Thimerosal	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
51-58	Phosphatidyl glycerol	Brij 98	Acetate	Benzyl alcohol	BHT	Glycerol	EDTA	Ethanol

				or paraben				
59-68	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
69-71	Phosphatidyl choline	Brij 98	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
72-73	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
74	Phosphatidyl choline	Tween 80	Acetate		BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
75	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
76	Phosphatidyl choline	Brij 98	Phosphate	Benzalkonium chloride	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
77	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol

78	Phosphatidyl choline	Brij 98	Phosphate	Benzalkonium chloride	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
79	Phosphatidyl choline	Brij 98	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
80	Phosphatidyl choline	Tween 80	Acetate		BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
81	Phosphatidyl choline	Tween 80	Acetate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
82-83	Phosphatidyl choline	Tween 80	Acetate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
84-88	Phosphatidyl choline	Tween 80	Acetate	Benzyl alcohol or paraben	BHA (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
89	Phosphatidyl choline	Tween 80	Acetate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
90-93	Phosphatidyl choline	Tween 80	Acetate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite	Glycerol	EDTA	Ethanol

					(0.500)			
94-96	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
97-98	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
99-100	Phosphatidyl choline	Tween 80	Phosphate		BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
101-103	Phosphatidyl choline	Tween 80	Acetate		BHT (0.200) sodium metabisulfite (0.500)		EDTA	
104	Phosphatidyl choline	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
105	Phosphatidyl choline		Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
106-108	Phosphatidyl choline	Tween 80	Phosphate		BHT (0.200) sodium metabisulfite (0.500)		EDTA	

109-116	Phosphatidyl glycerol and lysophospholipid	Brij 98	Acetate	Benzyl alcohol or paraben	BHT	Glycerol	EDTA	Ethanol
117-126	Phosphatidyl choline and lysophospholipid	Tween 80	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol
127-129	Phosphatidyl choline and lysophospholipid	Brij 98	Phosphate	Benzyl alcohol or paraben	BHT (0.200) sodium metabisulfite (0.500)	Glycerol	EDTA	Ethanol

Example Formulation 1

[0103] Formulation 1 comprises sphingomyelin (brain) (47.944 mg/g) as a lipid, Tween 80 (42.056mg/g) as a surfactant, lactate buffer (pH 4), benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (.0500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 2

[0104] Formulation 2 comprises sphingomyelin (brain) (53.750 mg/g) as a lipid, Tween 80 (31.250 mg/g) as a surfactant, lactate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (15.000 mg/g).

Example Formulation 3

[0105] Formulation 3 comprises sphingomyelin (brain) (90.561 mg/g) as a lipid, Tween 80 (79.439 mg/g) as a surfactant, lactate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 4

[0106] Formulation 4 comprises sphingomyelin (brain) (47.944 mg/g) as a lipid, Tween 80 (42.056 mg/g) as a surfactant, lactate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 5

[0107] Formulation 5 comprises sphingomyelin lauroyl (50.607 mg/g) as a lipid, Brij 98 (44.393 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (10.000 mg/g).

Example Formulation 6

[0108] Formulation 6 comprises sphingomyelin lauroyl (90.561 mg/g) as a lipid, Brij 98 (79.439 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 7

[0109] Formulation 7 comprises sphingomyelin lauroyl (49.276 mg/g) as a lipid, Brij 98 (79.439 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 8

[0110] Formulation 8 comprises phosphatidyl choline and phosphatidyl glycerol (53.750 mg/g) as a lipid, Brij 98 (31.250 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 9

[0111] Formulation 9 comprises phosphatidyl choline and phosphatidyl glycerol (90.561 mg/g) as a lipid, Brij 98 (79.439 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 10

[0112] Formulation 10 comprises phosphatidyl choline and phosphatidyl glycerol (41.351mg/g) as a lipid, Brij 98 (48.649 mg/g) as a surfactant, phosphate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 11

[0113] Formulation 11 comprises phosphatidyl choline and phosphatidyl glycerol (47.882 mg/g) as a lipid, Brij 98 (37.118 mg/g) as a surfactant, phosphate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 12

[0114] Formulation 12 comprises phosphatidyl choline and phosphatidyl glycerol (95.764 mg/g) as a lipid, Brij 98 (74.236 mg/g) as a surfactant, phosphate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 13

[0115] Formulation 13 comprises phosphatidyl choline and phosphatidylinositol (66.676 mg/g) as a lipid, Span 20 (24.324 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g), HTHQ (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (25.000 mg/g).

Example Formulation 14

[0116] Formulation 14 comprises phosphatidyl choline and phosphatidylinositol (62.027 mg/g) as a lipid, Span 20 (22.973 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 15

[0117] Formulation 15 comprises phosphatidyl choline and phosphatidylinositol (124.054 mg/g) as a lipid, Span 20 (45.946 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent, and ethanol (36.510 mg/g).

Example Formulation 16

[0118] Formulation 16 comprises phosphatidyl choline and phosphatidylinositol (62.687 mg/g) as a lipid, Span 20 (32.313 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl

alcohol or paraben (5.000 mg/g) as an antimicrobial agent, HTHQ (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 17

[0119] Formulation 17 comprises phosphatidyl choline and phosphatidic acid (41.853 mg/g) as a lipid, Tween 80 (43.147 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 18

[0120] Formulation 18 comprises phosphatidyl choline and phosphatidic acid (95.764 mg/g) as a lipid, Tween 80 (74.236 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 19

[0121] Formulation 19 comprises phosphatidyl choline and phosphatidic acid (47.882 mg/g) as a lipid, Brij 98 and Tween 80 (37.118 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, and EDTA (3.000 mg/g).

Example Formulation 20

[0122] Formulation 20 comprises phosphatidyl choline and phosphatidic acid (45.000 mg/g) as a lipid, Span 20 and Tween 80 (45.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, and EDTA (1.000 mg/g).

Example Formulation 21

[0123] Formulation 21 comprises phosphatidyl choline (31.935 mg/g) as a lipid, cremophor and Span 20 (58.065 mg/g) as a surfactant, lactate (pH 5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (15.000 mg/g).

Example Formulation 22

[0124] Formulation 22 comprises phosphatidyl choline (42.500 mg/g) as a lipid, cremophor and Tween 80 (42.500 mg/g) as a surfactant, lactate (pH 6.5) buffer, thimerosal

(5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 23

[0125] Formulation 23 comprises phosphatidyl choline (38.276 mg/g) as a lipid, cremophor (51.724 mg/g) as a surfactant, lactate (pH 4) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (36.510 mg/g) .

Example Formulation 24

[0126] Formulation 24 comprises phosphatidyl choline (42.500 mg/g) as a lipid, cremophor (42.500 mg/g) as a surfactant, lactate (pH 4) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (15.000 mg/g).

Example Formulation 25

[0127] Formulation 25 comprises phosphatidyl choline (85.000 mg/g) as a lipid, cremophor (85.000 mg/g) as a surfactant, lactate (pH 4) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 26

[0128] Formulation 26 comprises phosphatidyl choline (38.276 mg/g) as a lipid, cremophor (51.276 mg/g) as a surfactant, lactate (pH 5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, and EDTA (1.000 mg/g) as a chelating agent.

Example Formulation 27

[0129] Formulation 27 comprises phosphatidyl choline (36.429 mg/g) as a lipid, cremophor (48.571 mg/g) as a surfactant, lactate (pH 5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 28

[0130] Formulation 28 comprises phosphatidyl choline (72.299 mg/g) as a lipid, cremophor (97.701 mg/g) as a surfactant, lactate (pH 5) buffer, thimerosal (5.000 mg/g) as an

antimicrobial agent, BHA (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (15.000 mg/g).

Example Formulation 29

[0131] Formulation 29 comprises phosphatidyl ethanolamine (46.250 mg/g) as a lipid, Tween 80 (46.250 mg/g) as a surfactant, phosphate (pH 6.5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (20.000 mg/g).

Example Formulation 30

[0132] Formulation 30 comprises phosphatidyl ethanolamine (38.804 mg/g) as a lipid, Tween 80 (46.196 mg/g) as a surfactant, phosphate (pH 6.5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as an antioxidant, glycerol (15.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 31

[0133] Formulation 31 comprises phosphatidyl ethanolamine (36.667 mg/g) as a lipid, Brij 98 and Tween 80 (33.333 mg/g) as a surfactant, phosphate (pH 6.5) buffer, thimerosal (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 32

[0134] Formulation 32 comprises phosphatidyl glycerol (23.333 mg/g) as a lipid, cremophor and Brij 98 (66.667 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, and EDTA (3.000 mg/g) as a chelating agent .

Example Formulation 33

[0135] Formulation 33 comprises phosphatidyl glycerol (45.833 mg/g) as a lipid, Brij 98 (41.667 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 34

[0136] Formulation 34 comprises phosphatidyl glycerol (31.957 mg/g) as a lipid, Brij 98 (38.043 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 35

[0137] Formulation 35 comprises phosphatidyl glycerol (47.143 mg/g) as a lipid, Brij 98 (42.857 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (1.000 mg/g) as a chelating agent, and ethanol (25.000 mg/g).

Example Formulation 36

[0138] Formulation 36 comprises phosphatidyl glycerol (96.905 mg/g) as a lipid, Brij 98 (88.095 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (20.000 mg/g).

Example Formulation 37

[0139] Formulation 37 comprises phosphatidyl glycerol (31.957 mg/g) as a lipid, Brij 98 (38.043) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 38

[0140] Formulation 38 comprises phosphatidyl ethanolamine (35.455 mg/g) as a lipid, cremophor (54.545 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 39

[0141] Formulation 39 comprises phosphatidyl ethanolamine (84.457 mg/g) as a lipid, cremophor (100.543 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite

(0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 40

[0142] Formulation 40 comprises phosphatidyl ethanolamine (89.048 mg/g) as a lipid, cremophor (80.952 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g), BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 41

[0143] Formulation 41 comprises phosphatidyl glycerol (41.087 mg/g) as a lipid, Tween 80 (48.913 mg/g) as a surfactant, propionate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (36.510 mg/g).

Example Formulation 42

[0144] Formulation 42 comprises phosphatidyl glycerol (45.280 mg/g) as a lipid, Tween 80 (39.720 mg/g) as a surfactant, propionate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 43

[0145] Formulation 43 comprises phosphatidyl glycerol (107.500 mg/g) as a lipid, Tween 80 (62.500 mg/g) as a surfactant, propionate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 44

[0146] Formulation 44 comprises phosphatidyl glycerol (77.243 mg/g) as a lipid, Tween 80 (67.757 mg/g) as a surfactant, propionate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 45

[0147] Formulation 45 comprises phosphatidyl glycerol (45.280 mg/g) as a lipid, Tween 80 (39.720 mg/g) as a surfactant, propionate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 46

[0148] Formulation 46 comprises phosphatidyl glycerol (90.561 mg/g) as a lipid, Tween 80 (79.439 mg/g) as a surfactant, propionate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 47

[0149] Formulation 47 comprises phosphatidyl glycerol (47.944 mg/g) as a lipid, Tween 80 (42.056 mg/g) as a surfactant, propionate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, EDTA (3.000 mg/g) as a chelating agent, and ethanol (10.000 mg/g).

Example Formulation 48

[0150] Formulation 48 comprises phosphatidyl serine (50.607 mg/g) as a lipid, Brij 98 (44.393 mg/g) as a surfactant, phosphate (pH 5.5) buffer, thimerasol (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), and EDTA (1.000 mg/g) as a chelating agent.

Example Formulation 49

[0151] Formulation 49 comprises phosphatidyl serine (107.500 mg/g) as a lipid, Brij 98 (62.500 mg/g) as a surfactant, phosphate (pH 5.5) buffer, thimerasol (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 50

[0152] Formulation 50 comprises phosphatidyl serine (47.944 mg/g) as a lipid, Brij 98 (42.056 mg/g) as a surfactant, phosphate (pH 5.5) buffer, thimerasol (5.000 mg/g) as an antimicrobial agent, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as

antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 51

[0153] Formulation 51 comprises phosphatidyl glycerol (46.364 mg/g) as a lipid, Brij 98 (38.636 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (25.000 mg/g).

Example Formulation 52

[0154] Formulation 52 comprises phosphatidyl glycerol (46.364 mg/g) as a lipid, Brij 98 (38.636 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (20.000 mg/g).

Example Formulation 53

[0155] Formulation 53 comprises phosphatidyl glycerol (46.098 mg/g) as a lipid, Brij 98 (43.902 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (15.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 54

[0156] Formulation 54 comprises phosphatidyl glycerol (43.537 mg/g) as a lipid, Brij 98 (41.463 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 55

[0157] Formulation 55 comprises phosphatidyl glycerol (45.000 mg/g) as a lipid, Brij 98 (45.000 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 56

[0158] Formulation 56 comprises phosphatidyl glycerol (59.492 mg/g) as a lipid, Brij 98 (30.508 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000

mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 57

[0159] Formulation 57 comprises phosphatidyl glycerol (39.054 mg/g) as a lipid, Brij 98 (45.946 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 58

[0160] Formulation 58 comprises phosphatidyl glycerol (35.854 mg/g) as a lipid, Brij 98 (34.146 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 59

[0161] Formulation 59 comprises phosphatidyl choline (50.000 mg/g) as a lipid, Tween 80 (40.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 60

[0162] Formulation 60 comprises phosphatidyl choline (38.571 mg/g) as a lipid, Tween 80 (51.429 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 61

[0163] Formulation 61 comprises phosphatidyl choline (41.954 mg/g) as phospholipid, Tween 80 (50.546 mg/g) as surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 62

[0164] Formulation 62 comprises phosphatidyl choline (42.632 mg/g) as a lipid, Tween 80 (47.368 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 63

[0165] Formulation 63 comprises phosphatidyl choline (46.098 mg/g) as a lipid, Tween 80 (43.902 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 64

[0166] Formulation 64 comprises phosphatidyl choline (39.721 mg/g) as a lipid, Tween 80 (50.279 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 65

[0167] Formulation 65 comprises phosphatidyl choline (44.198 mg/g) as a lipid, Tween 80 (50.802 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 66

[0168] Formulation 66 comprises phosphatidyl choline (46.453 mg/g) as a lipid, Tween 80 (51.047 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 67

[0169] Formulation 67 comprises phosphatidyl choline (51.221 mg/g) as a lipid, Tween 80 (43.779 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 68

[0170] Formulation 68 comprises phosphatidyl choline (54.167 mg/g) as a lipid, Tween 80 (43.333 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 69

[0171] Formulation 69 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 69 is an emulsion.

Example Formulation 70

[0172] Formulation 70 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 70 is a suspension.

Example Formulation 71

[0173] Formulation 71 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 72

[0174] Formulation 72 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 72 is an emulsion.

Example Formulation 73

[0175] Formulation 73 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 73 is a suspension.

Example Formulation 74

[0176] Formulation 74 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, acetate (pH 5.5) buffer, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 75

[0177] Formulation 75 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 76

[0178] Formulation 76 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Brij 98 (50.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzalkonium chloride (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 77

[0179] Formulation 77 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 78

[0180] Formulation 78 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzalkonium chloride (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 79

[0181] Formulation 79 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 80

[0182] Formulation 80 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, acetate (pH 5.5) buffer, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 81

[0183] Formulation 81 comprises phosphatidyl choline (40.000 mg/g) as a lipid, Tween 80 (50.000 mg/g) as a surfactant, acetate (pH 5.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 82

[0184] Formulation 82 comprises phosphatidyl choline (44.444 mg/g) as a lipid, Tween 80 (55.556 mg/g) as a surfactant, acetate (pH 5.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 83

[0185] Formulation 83 comprises phosphatidyl choline (66.440 mg/g) as a lipid, Tween 80 (23.560 mg/g) as a surfactant, acetate (pH 5.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 84

[0186] Formulation 84 comprises phosphatidyl choline (54.000 mg/g) as a lipid, Tween 80 (36.000 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 85

[0187] Formulation 85 comprises phosphatidyl choline (50.000 mg/g) as a lipid, Tween 80 (40.000 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 86

[0188] Formulation 86 comprises phosphatidyl choline (48.611 mg/g) as a lipid, Tween 80 (38.889 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 87

[0189] Formulation 87 comprises phosphatidyl choline (46.575 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 87 is an emulsion.

Example Formulation 88

[0190] Formulation 88 comprises phosphatidyl choline (46.575 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 88 is suspension.

Example Formulation 89

[0191] Formulation 89 comprises phosphatidyl choline (46.575 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 90

[0192] Formulation 90 comprises phosphatidyl choline (50.000 mg/g) as a lipid, Tween 80 (40.000 mg/g) as a surfactant, acetate (pH 4.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 91

[0193] Formulation 91 comprises phosphatidyl choline (94.444 mg/g) as a lipid, Tween 80 (75.556 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 92

[0194] Formulation 92 comprises phosphatidyl choline (46.712 mg/g) as a lipid, Tween 80 (38.288 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 93

[0195] Formulation 93 comprises phosphatidyl choline (48.889 mg/g) as a lipid, Tween 80 (39.111 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 94

[0196] Formulation 94 comprises phosphatidyl choline (39.721 mg/g) as a lipid, Tween 80 (50.279 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.25 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 95

[0197] Formulation 95 comprises phosphatidyl choline (90.000 mg/g) as a lipid, phosphate buffer (pH 6.5), benzyl alcohol or paraben as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 96

[0198] Formulation 96 comprises phosphatidyl choline (68.700 mg/g) as a lipid, Tween 80 (8.500 mg/g) as a surfactant, phosphate (pH 7.5) buffer, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, glycerol (30.000 mg/g), EDTA (1.000 mg/g) as a chelating agent, and ethanol (36.51 mg/g).

Example Formulation 97

[0199] Formulation 97 comprises phosphatidyl choline (71.460 mg/g) as a lipid, Tween 80 (4.720 mg/g) as a surfactant, phosphate (pH 7.5) buffer, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, glycerol (50.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (35.000 mg/g).

Example Formulation 98

[0200] Formulation 98 comprises phosphatidyl choline (71.460 mg/g) as a lipid, Tween 80 (4.720 mg/g) as a surfactant, phosphate (pH 7.8) buffer, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, glycerol (15.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (35.000 mg/g).

Example Formulation 99

[0201] Formulation 99 comprises phosphatidyl choline (71.460 mg/g) as a lipid, Tween 80 (4.720 mg/g) as a surfactant, phosphate (pH 7.8) buffer, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (50.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (15.000 mg/g).

Example Formulation 100

[0202] Formulation 100 comprises phosphatidyl choline (71.4600 mg/g) as a lipid, Tween 80 (4.720 mg/g) as a surfactant, phosphate (pH 7.5) buffer, BHA (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (50.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (35.000 mg/g).

Example Formulation 101

[0203] Formulation 101 comprises phosphatidyl choline (46.575 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, phosphate (pH 4) buffer, BHT (0.500 mg/g) and sodium metabisulfite (0.200mg/g) as antioxidants, and EDTA (3.000 mg/g) as a chelating agent. Example formulation 101 is an emulsion.

Example Formulation 102

[0204] Formulation 102 comprises phosphatidyl choline (46.575 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, phosphate (pH 4) buffer, BHT (0.500 mg/g) and sodium

metabisulfite (0.200mg/g) as antioxidants, and EDTA (3.000 mg/g). Example formulation 102 is a suspension.

Example Formulation 103

[0205] Formulation 103 comprises phosphatidyl choline (54.643 mg/g) as a lipid, Tween 80 (30.357 mg/g) as a surfactant, phosphate (pH 4) buffer, BHA (0.500 mg/g) and sodium metabisulfite (0.200mg/g) as antioxidants, and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 104

[0206] Formulation 104 comprises phosphatidyl choline (39.72 mg/g)as a lipid, Tween 80 (50.279 mg/g) as surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.00 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g) as emollient, EDTA (3.000 mg/g) as the chelating agent, and ethanol (30.000 mg/g).

Example Formulation 105

[0207] Formulation 105 comprises phosphatidyl choline (90.00 mg/g) as a lipid, phosphate (pH 6.5) buffer, benzyl alcohol or paraben as antimicrobial (5.000 mg/s), BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g) as emollient, EDTA (3.000 mg/g) as the chelating agent, and ethanol (30.000 mg/g).

Example Formulation 106

[0208] Formulation 106 comprises phosphatidyl choline (46.57 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, phosphate (pH 4) buffer, BHT (0.500 mg/g) and sodium metabisulfite (0.200mg/g) as antioxidants, and EDTA (3.000 mg/g) as the chelating agent. Formulation 106 is formulated as an emulsion.

Example Formulation 107

[0209] Formulation 107 comprises phosphatidyl choline (46.57 mg/g) as a lipid, Tween 80 (38.425 mg/g) as a surfactant, phosphate (pH 4) buffer, BHT (0.500 mg/g) and sodium metabisulfite (0.200mg/g) as antioxidants, and EDTA (3.000 mg/g) as the chelating agent. Formulation 107 as a suspension.

Example Formulation 108

[0210] Formulation 108 comprises phosphatidyl choline (54.64 mg/g)as a lipid, Tween 80 (30.357 mg/g) as a surfactant, phosphate (pH 4) buffer, BHA (0.500 mg/g) and sodium metabisulfite (0.200mg/g) as antioxidants, EDTA (3.000 mg/g) as the chelating agent.

Example Formulation 109

[0211] Formulation 109 comprises phosphatidyl glycerol and lysophospholipid (46.364 mg/g) as a lipid, Brij 98 (38.636 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (25.000 mg/g).

Example Formulation 110

[0212] Formulation 110 comprises phosphatidyl glycerol and lysophospholipid (46.364 mg/g) as a lipid, Brij 98 (38.636 mg/g) as a surfactant, acetate (pH 4) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (20.000 mg/g).

Example Formulation 111

[0213] Formulation 111 comprises phosphatidyl glycerol and lysophospholipid (46.098 mg/g) as a lipid, Brij 98 (43.902 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (15.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 112

[0214] Formulation 112 comprises phosphatidyl glycerol and lysophospholipid (43.537 mg/g) as a lipid, Brij 98 (41.463 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 113

[0215] Formulation 113 comprises phosphatidyl glycerol and lysophospholipid (45.000 mg/g) as a lipid, Brij 98 (45.000 mg/g) as a surfactant, acetate (pH 5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 114

[0216] Formulation 114 comprises phosphatidyl glycerol and lysophospholipid (59.492 mg/g) as a lipid, Brij 98 (30.508 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 115

[0217] Formulation 115 comprises phosphatidyl glycerol and lysophospholipid (39.054 mg/g) as a lipid, Brij 98 (45.946 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 116

[0218] Formulation 116 comprises phosphatidyl glycerol and lysophospholipid (35.854 mg/g) as a lipid, Brij 98 (34.146 mg/g) as a surfactant, acetate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) as an antioxidant, glycerol (30.000 mg/g), and EDTA (3.000 mg/g) as a chelating agent.

Example Formulation 117

[0219] Formulation 117 comprises phosphatidyl choline and lysophospholipid (50.000 mg/g) as a lipid, Tween 80 (40.000 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 118

[0220] Formulation 118 comprises phosphatidyl choline and lysophospholipid (38.571 mg/g) as a lipid, Tween 80 (51.429 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 119

[0221] Formulation 119 comprises phosphatidyl choline and lysophospholipid (41.954 mg/g) as phospholipid, Tween 80 (50.546 mg/g) as surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g), and ethanol (30.000 mg/g).

Example Formulation 120

[0222] Formulation 120 comprises phosphatidyl choline and lysophospholipid (42.632 mg/g) as a lipid, Tween 80 (47.368 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 121

[0223] Formulation 121 comprises phosphatidyl choline and lysophospholipid (46.098 mg/g) as a lipid, Tween 80 (43.902 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 122

[0224] Formulation 122 comprises phosphatidyl choline and lysophospholipid (39.721 mg/g) as a lipid, Tween 80 (50.279 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 123

[0225] Formulation 123 comprises phosphatidyl choline and lysophospholipid (44.198 mg/g) as a lipid, Tween 80 (50.802 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 124

[0226] Formulation 124 comprises phosphatidyl choline and lysophospholipid (46.453 mg/g) as a lipid, Tween 80 (51.047 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 125

[0227] Formulation 125 comprises phosphatidyl choline and lysophospholipid (51.221 mg/g) as a lipid, Tween 80 (43.779 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 126

[0228] Formulation 126 comprises phosphatidyl choline (54.167 mg/g) as a lipid, Tween 80 (43.333 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

Example Formulation 127

[0229] Formulation 127 comprises phosphatidyl choline and lysophospholipid (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 69 is an emulsion.

Example Formulation 128

[0230] Formulation 128 comprises phosphatidyl choline and lysophospholipid (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g). Example formulation 70 is a suspension.

Example Formulation 129

[0231] Formulation 129 comprises phosphatidyl choline and lysophospholipid (66.440 mg/g) as a lipid, Brij 98 (23.560 mg/g) as a surfactant, phosphate (pH 6.5) buffer, benzyl alcohol or paraben (5.000 mg/g) as an antimicrobial, BHT (0.200 mg/g) and sodium metabisulfite (0.500 mg/g) as antioxidants, glycerol (30.000 mg/g), EDTA (3.000 mg/g) as a chelating agent, and ethanol (30.000 mg/g).

[0232] It will be understood that the exact amounts of the components of the formula may be adjusted slightly without departing from the scope of the invention. For example, in each

of the above formulations, the amount antimicrobial be anywhere from about 1 mg/g to about 15 mg/g, or about 5 m/g to about 12 mg/g, or 5.25 mg/g, 6, mg/6, 7 mg/g, 8 mg/g, 9 mg/g, 10 mg/g, or 10.25 mg/g. Furthermore, the antimicrobial can be a combination of ingredients, for example benzyl alcohol and parabenes (e.g., ethyl and/or propyl).

[0233] Example Formulations 1 through 129 may also optionally include thickeners such as pectin, xanthan gum, HPMC gel, methylcellulose or carbopol.

5.2 Example 2: DIRACTIN® Clinical Studies

[0234] Clinical studies directed to DIRACTIN® (ketoprofen in TRANSFERSOME® gel) were performed in the United States and in Europe. Table 9 provides details of the number of sites patients and the like in the European and US studies.

Table 9: Comparative evaluation of various clinical studies conducted

	Sites	Screen Failures	Random	PP	Discont.	Screen F. Rate	PP per site	Rel. Discont.
US (-06)	37	329	555	376/452	105	59%	10/12	19%
EU (-03)	71	192	1399	1163	143	14%	16	10%

5.2.1. United States Study

[0235] A multicentre, randomized, double-blind, placebo-controlled study of safety and efficacy of epicutaneously applied DIRACTIN® (ketoprofen in TRANSFERSOME® gel) was conducted in the United states for the treatment of osteoarthritis of the knee. The study was conducted from Q2/2008 to Q2/2009 and included 555 patients in 37 study centres. Patients were treated twice daily at approximately 12 hour intervals for 12 weeks with either:

(1) 100 mg ketoprofen (KT) in DIRACTIN® gel, epicutaneously (e.c.) or

(2) Placebo gel with volume matched with 100 mg KT in DIRACTIN®, e.c.

[0236] The DIRACTIN® gel and the placebo gel included transfersomes in accordance with the descriptions provided herein. Rescue pain medication was provided in the amount of 500 mg acetaminophen up to four times a day, total 2 g.

[0237] The data from these studies established that the placebo transfersomes (i.e., transfersomes of the technology described herein) were active. Data from the US study are shown in Figures 1-5. Figure 1 shows Mann-Whitney statistics and continuous responder

analysis of pain measurements in patients. Figure 2 provides the incidences of Adverse Events by organ class system. Subgroup analysis results for WOMAC pain intensity are shown in Figures 3 and 4; with Figure 3 at a baseline of >5.5 and Figure for at baseline ≤5.5. Descriptive statistics for the use of rescue medication are provided in Figure 5.

5.2.2. European Study

[0238] A multicentre, randomized, double-blind, placebo-controlled study of safety and efficacy of epicutaneously applied DIRACTIN® (ketoprofen in TRANSFERSOME® gel) was also conducted in Europe for the treatment of osteoarthritis of the knee. The study was conducted from Q2/2008 to Q2/2009 and included 1,399 patients in 71 study centres (in Czech Republic, Germany, Poland, and UK). Patients were treated twice daily at approximately 12 hour intervals for 12 weeks with either:

(1) 50 mg ketoprofen (KT) in DIRACTIN® gel, epicutaneously (e.c.)

(2) Placebo gel with volume matched with 50 mg KT in DIRACTIN®, e.c.

(3) 100 mg ketoprofen (KT) in DIRACTIN® gel, e.c.

(4) Placebo gel with volume matched with 100 mg KT in DIRACTIN®, e.c.

(5) 100 mg celecoxib capsule (CELEBREX®, Pfizer), oral

(6) Placebo capsule, matching celecoxib, oral

[0239] The DIRACTIN® gel and the placebo gel included transfersomes in accordance with the descriptions provided herein. Rescue pain medication was provided in the amount of 500 mg acetaminophen up to four times a day, total 2 g.

[0240] A schematic illustrating the study design is shown on Figure 6 and an illustration showing the statistical evaluations are shown in Figure 7.

[0241] The data from these studies established that the placebo transfersomes (i.e., transfersomes of the technology described herein) were active. Data from the European study are shown in Figures 8-17. Figures 8-9 show Mann-Whitney statistics and continuous responder analysis of pain measurements in patients, with Figure 8 showing results for the 100 mg dose of KT and placebo gel and Figure 9 showing results for the 50 mg dose of KT and placebo gel. Figures 10 and 11 show WOMAC pain and Mann-Whitney statistics for the 100 mg celecoxib capsule (CELEBREX®, Pfizer) and the oral placebo. Figure 12 shows Mann-Whitney statistics and continuous responder analysis of pain measurements in patients for the 50 mg dose of KT vs. the 100 mg celecoxib capsule (CELEBREX®, Pfizer). Figure 13 shows Mann-Whitney statistics for the 100 mg dose of KT vs. the oral placebo and Figure

14 shows Mann-Whitney statistics for the 50 mg dose of KT vs. the oral placebo. Figure 15 shows Mann-Whitney statistics for the 100 mg dose of KT vs. 100 mg celecoxib capsule (CELEBREX®, Pfizer). Figure 16 shows Mann-Whitney statistics for the 100 mg dose of KT vs. the oral placebo, using the "per protocol population" instead of "intention to treat" (ITT). Figure 17 shows possibly treatment related adverse events (Aes) observed in the study.

5.2.3. Inter-studies Results and Conclusions

[0242] The combined results of the US and European studies establish that the placebo gel (transfersomes gel) is equivalent or better than the ketoprofen-containing gel, and that each have similar efficacy to oral celecoxib. All three of these products are shown to be superior to oral placebo. The effectiveness of the placebo gel (transfersomes gel) was similar to oral drugs acting on Cox-II but had substantially lower side effects liability. Figure 18 shows the average group change for the various treatments at week 6 and 12 of the studies. Figure 19 shows the effect of the placebo response in published data and by the placebo gel that is the subject of the invention.

5.3 Example 3: Clinical Trials for Transfersomes for Inflammatory Dermatoses

[0243] A multicentre, randomized, double-blind, placebo-controlled study of safety and efficacy of IDEA-070 (transfersome spray containing ketoprofen) was conducted in the Germany for the treatment of inflammatory dermatological diseases. The study was conducted from Q1/2005 to Q4/2005 and included 240 patients in 7 study centres. The target indications for the study were atopic eczema, dishydrotic hand eczema, plaque type psoriasis, seborrheic eczema, and acne vulgaris. The treatment group used in the study received 0.24 mg ketoprofen per cm^2 skin in IDEA-070 spray, e.c., b.i.d. and the controls received a topical placebo (randomisation: IDEA-070/placebo: 2/1). Transfersomes used in this study were made in accordance with transfersomes as described herein. The primary objectives of the study were to evaluate the effects of IDEA-070 compared to a placebo in patients with atopic eczema, dishydrotic hand eczema, plaque type psoriasis, seborrheic eczema, and acne vulgaris using the Investigator Global Assessments score (IGA) and the secondary objectives were to evaluate the efficacy of IDEA-070 compared to a placebo using the Patient Global

Assessments score (PGA) and indication specific scores (SCORAD, DASI, PASI, GAGS) as well as to test the safety of IDEA-070.

[0244] Patient inclusion in the study required that the patient (1) had one of the following diseases (mild to moderate): atopic eczema, dishydrotic hand eczema, plaque type psoriasis (hyperkeratoses removed before treatment by urea or salicylic acid), seborrheic eczema in the face or head), or acne vulgaris; (2) was aged 18-80 years; and (3) that women of childbearing potential were using a reliable method of contraception. Patients meeting any of the following criteria were excluded from the study: Systemic therapy for skin diseases within 2 weeks prior to start of treatment; UV therapy within 4 weeks prior to start of treatment; Chronic or acute illness requiring systemic anti-inflammatory treatment; Skin cancer and precancerous skin lesions; History of peptic ulcers or gastric intolerance with NSAIDs; History of asthma bronchiale; History of chronic airway infection; History of renal insufficiency; Thrombocytopathia; Immunosuppressants (e.g., corticosteroids) within 2 weeks prior to start of treatment; Known sensitisation to NSAIDs; Pregnancy or lactation; Mental disorders.

[0245] Table 10 summarizes the study population used in the study.

Table 10:

	Placebo	IDEA-070	All
Acne	17	33	**50**
Atopic E.	17	31	**48**
Dishydrotic E.	18	34	**52**
Psoriasis	16	35	**51**
Seborrheic E.	14	34	**48**
		Total	**249**

[0246] The data from these studies established that the placebo transfersomes (i.e., transfersomes of the technology described herein) were active. Figures 20-23 provide results of the study. Figure 20 shows the IGA score for the five main objective indications. As shown of Figure 20 there was no significant difference between IDEA-070 and placebo for any of the indications except for seborrheic eczema, in which the placebo gel showed a more marked improvement that TDT 070 with a p value of $p = 0.031$. Figures 21-23 show the IGA scores at week 1, 2 and 3 for seborrheic eczema, psoriasis, psoriasis area and severity index (PASI), and erythema, respectively.

[0247] Adverse events by indication observed in the study are shown in Table 11.

Table 11:

	Placebo	IDEA-070
Akne	17.6 %	24.2 %
Atopic E.	41.2 %	32.3 %
Dishydrotic E.	16.7 %	20.6 %
Psoriasis	12.5 %	25.7 %
Seborrheic E.	7.1 %	23.5 %
All	**19.5 %**	**25.1 %**

[0248] Adverse events by system organ class- skin and subcutaneous tissue are shown in Table 12.

Table 12

	Placebo	IDEA-070
Akne	0	1
Atopic E.	0	5
Dishydrotic E.	0	1
Psoriasis	1	4
Seborrheic E.	0	0
All	**1**	**11**

5.4 Example 4: Sequestration of Arachidonic Acid

[0249] Assays were performed to assess the effect of transfersomes arachidonic acid sequestration. The assays used in these studies involved using arachidonic acid as a substrate and measuring cylclooxygenase activity as an indicator of arachidonic acid sequestration Other assays could be used to measure/analyze arachidonic acid sequestration. For example sequestration could be measured using radiolabeled arachidonic acid (or another lipid), adding the transfersomes to sequester the lipid, centrifuging to separate the transfersomes (or using another method of separating transfersomes, such as filtration) and measuring the radiolabeled lipid in the transfersomes as an indicator of sequestration.

[0250] Transfersomes used in this study were made in accordance with the transfersomes described herein.

[0251] Representative results from the COX inhibition / Sequestration assays are shown in Figures 25-26. Figure 25 shows a double reciprocal plot of COX reaction velocity versus arachidonic acid concentration for a control, 50 μM ketoprofen and 100 μM transfersomes.

The differences between the results of the control and the 100 μM transfersomes indicate sequestration of the arachidonic acid substrate. Figure 26 shows the COX reaction velocity using 16 μM arachidonic acid and increasing amounts of transfersomes. The saturation at between 50-70 μM transfersomes suggests that the critical sequestration capacity of the transfersomes occurs in this range (as marked on the figure).

5.5 Example 5: Sequestration of Other Lipids

[0252] Assays are performed to assess the effect of transfersomes on other lipids. Other lipids include cholesterol, mediators of pain and inflammation (e.g., such as prostaglandins, prostaglandin precursors and leukotrienes. The transfersomes are effective in sequestering identified lipids.

CLAIMS

1. Use of a vesicular formulation comprising one or more phospholipids and one or more non-ionic surfactants in the manufacture of a medicament for the treatment of inflammatory dermatoses disorders or fungal infection, in which the formulation does not comprise any non-lipid, non-surfactant pharmaceutically active agent and in which the medicament is topically applied.

2. Use of a vesicular formulation according to Claim 1, for the treatment of atopic eczema, dishydrotic hand eczema, plaque type psoriasis, seborrheic eczema, or acne vulgaris.

3. Use of a vesicular formulation according to Claim 1 or 2, in which the formulation is a cream, lotion, ointment, gel, solution, spray, lacquer or film forming solution.

4. Use of a vesicular formulation according to Claim 1, 2 or 3, in which the ratio of phospholipid to surfactant is about 1:3 to about 30:1.

5. Use of a vesicular formulation according to any preceding claim, in which the formulation contains 2.0 to 10.0% by weight phospholipid.

6. Use of a vesicular formulation according to any preceding claim, in which the formulation contains 0.2 to 0.5% by weight surfactant.

7. Use of a vesicular formulation according to any of Claims 1 to 5, in which the formulation contains 0.2% to 0.5% by weight surfactant.

8. Use of a vesicular formulation according to any of Claims 1 to 6, in which the phospholipid is phosphatidylcholine.

9. Use of a vesicular formulation according to any preceding claim, in which the surfactant is a nonionic surfactant selected from the group consisting of: polyoxyethylene sorbitans, polyhydroxyethylene stearates or polyhydroxethylene laurylethers.

10. Use of a vesicular formulation according to any preceding claim, in which the surfactant is polysorbate 80 (Tween 80).