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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 August 2012 (16.08.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/109151 A1

(51) International Patent Classification:
A61K 9/127 (2006.01)

(21) International Application Number:
PCT/US2012/023992

(22) International Filing Date:
6 February 2012 (06.02.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
13/022,385 7 February 2011 (07.02.2011) US

(71) Applicant: **PROFESSIONAL COMPOUNDING CENTERS OF AMERICA, LTD.** [US/US]; 9901 South Wilcrest Drive, Houston, TX 77099 (US).

(72) Inventors: **BASSANI, August, S.**; 25803 Pepper Bend Lane, Katy, TX 77494 (US). **BANOV, Daniel**; 1302 Gray Hills Court, Sugar Land, TX 77479 (US).

(74) Agents: **McFARLAND, Elena, K.** et al.; Shook, Hardy & Bacon, L.L.P., 2555 Grand Blvd., Kansas City, MO 64108-2613 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, ZA, ZM, ZW.

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

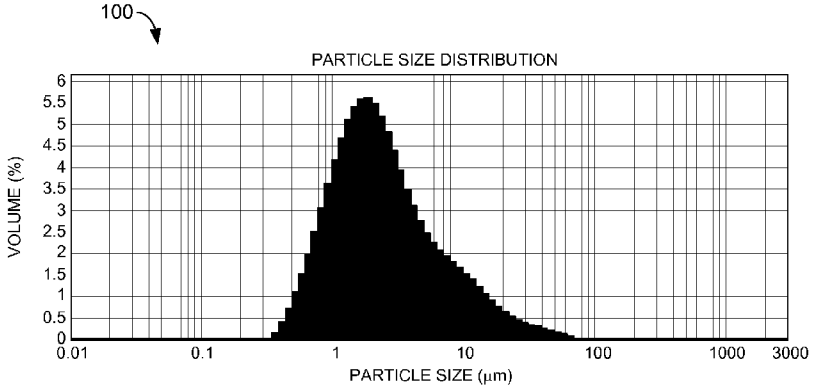
Published:

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

WO 2012/109151 A1

(54) Title: PERMEATION ENHANCERS WITH LIPOSOMES FOR TOPICAL FORMULATIONS

FIG. 1.



(57) Abstract: Method for producing liposomes in a composition for skin permeation are provided. A composition that includes water, skin lipids, butters having linoleic acid and linolenic acid, Pracaxi oil, Plukenetia Volubilis seed oil, and phospholipids is provided. The composition is dispersed in a vessel using a high shear homogenizer. Negative pressure is created in the vessel such that liposomes of 5-20 microns are produced thereby providing for increased skin permeation of active ingredients added to the composition.

PERMEATION ENHANCERS WITH LIPOSOMES FOR TOPICAL FORMULATIONS

BACKGROUND OF THE INVENTION

Typically, active ingredients, such as drugs, are not easily permeated through the skin when used in topical cosmetic products or pharmaceutical formulations that are topically delivered. Further, some active ingredients may need to be pre-encapsulated. Additionally, while acids such as behenic acid and oleic acid have traditionally been added to topical formulations to assist with the delivery of drugs through the skin, these acids can be extremely irritating to the skin when used alone. In addition to high levels of irritancy, formulations typically used to enhance permeation through the skin can be unstable.

SUMMARY OF THE INVENTION

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter. Embodiments of the present invention are directed to a composition that enhances permeation of an active ingredient, such as a drug, through the skin. The composition may be used with, for example, topical cosmetics or pharmaceutical formulations that are topically applied. Methods of preparing such a composition are also described herein.

In one embodiment, a method for producing liposomes in a composition for skin permeation is provided, wherein the liposomes have a small particle size. The method includes providing the composition comprising water, one or more skin lipids, one or more butters having linoleic acid and linolenic acid, Pracaxi oil, Plukenetia Volubilis Seed oil, and one or more phospholipids. The method further includes dispersing the composition utilizing a high shear homogenizer in a vessel, and creating negative pressure in the vessel to produce a final composition. Liposomes are produced and are present in the final composition. The liposomes have particle sizes of around 5-20 microns to improve skin permeation of an active ingredient formulation to which the final composition is added.

In another embodiment, a natural composition used for skin permeation is provided. The natural composition includes one or more phospholipids, Pracaxi oil, one or

more skin lipids, and a butter having linoleic acid and linolenic acid. When components of the composition are combined, liposomes are produced in the composition having particle sizes around 5-20 microns such that skin permeation is increased by way of small particle sizes.

In yet another embodiment, a method is provided for producing liposomes in a composition used for skin permeation. The method includes providing a natural composition, the natural composition comprising one or more phospholipids, and one or more oils having essential fatty acids, behenic acid, and oleic acid, wherein one of the one or more oils is Pracaxi oil. The method further includes combining the one or more phospholipids and the one or more oils, and in a vessel, dispersing the composition at speeds up to 5,000 rotations per minute (RPM). Additionally, the method includes creating negative pressure in the vessel to produce liposomes having particle sizes around 5-20 microns.

Additional aspects of the invention, together with the advantages and novel features appurtenant thereto, will be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned from the practice of the invention. The objects and advantages of the invention may be realized and attained by means, instrumentalities, and combinations particular pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWING

Illustrative embodiments of the present invention are described in detail below with reference to the attached drawing figures, and wherein:

FIG. 1 is a logarithmic graph illustrating particle size distribution, in accordance with an embodiment of the present invention;

FIG. 2 illustrates a microscopy picture showing the distribution of liposome particle sizes, in accordance with an embodiment of the present invention;

FIG. 3 illustrates mean flux over time for an exemplary formulation, in accordance with an embodiment of the present invention;

FIG. 4 illustrates the percent of the applied dose of an exemplary formulation absorbed, in accordance with an embodiment of the present invention; and

FIG. 5 illustrates a method for preparing a natural composition to be used for skin permeation, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention are directed to a composition of ingredients that, in one embodiment is a natural composition or formulation. The composition contains one or more naturally occurring substances, including one or more phospholipids, one or more oils rich in essential fatty acids, behenic acid, and oleic acid, one or more skin lipids, and one or more butters rich in linoleic acid and linolenic acid. This composition, in one embodiment, is used as a penetration enhancer for a number of different compounds, including topical cosmetics and pharmaceutical formulations. While the composition is safe and effective, it is comprised of natural ingredients that assist with penetration of an active ingredient through the skin.

The fatty acid microparticle composition described herein contains, among other components, behenic acid, oleic acid, omega-3 fatty acids, and phospholipids. This composition may be produced under highly controlled production conditions using methods described herein, such as by using a high shear homogenizer, which results in a relatively uniform size distribution. For instance, in embodiments, the size of the particles is around 5-20 microns, which increases skin permeation of an active ingredient through synergism of all of the components. The composition is generally used for administering active ingredients through the skin, in addition to hydrating the skin by forming a semi-occlusive film on the skin by way of the unique mixture of ingredients.

The composition described herein may be formulated as a liquid or a semi-liquid, and as mentioned, acts as a penetration enhancer for active ingredients contained within a final product. The effect of the penetration enhancing composition, as described herein, occurs because of its presence in the final formulation. This eliminates the need for pre-encapsulation of the active ingredients. Additionally, this composition may be used at the pharmacy level, whereby a pharmacist would be able to add the composition to a cream or other topical formulation, at a certain percentage, thus providing penetration power to the topical formulation. This composition used for penetration enhancement is designed to be useable in a large variety of topical systems, with decreased concern for the stability and aesthetic properties of the final formulation.

While there is no official legal definition of the term “natural” as it relates to cosmetic ingredients, Ecocert, BDIH (the Federation of German Industries and Trading) and

the Soil Association both agree that the term implies a ban on the use of petrochemical derived ingredients, silicones, ethoxylated raw materials, and halogen organic compounds.

As mentioned, the composition described herein contains one or more naturally occurring substances, including one or more phospholipids, one or more oils rich in essential fatty acids, behenic acid, and oleic acid, one or more skin lipids, and one or more butters rich in linoleic acid and linolenic acid. These ingredients, together, act synergistically to increase the skin permeation of water and oil soluble products. The composition, which is a solution, may be added to a gel or emulsion at a given percent to give permeation power to the otherwise topical preparation. When the composition described herein is prepared, liposomes are formed from the fatty acids, including behenic acid and oleic acid that are present the one or more oils, and are stabilized by the phospholipids in the composition. More specifically, when the permeation enhancer composition described herein is added to water or a water-containing composition, liposomes are formed.

Liposomes are artificially prepared vesicles made of lipid bilayer, and have concentric phospholipid bilayers. In some embodiments, liposomes are filled with drugs or other active ingredients and used to deliver these drugs. Liposomes may be composed of naturally-derived phospholipids with mixed lipid chains or other surfactants. In embodiments of the present invention, the liposomes that are formed are used to deliver drugs or other active ingredients topically to the skin's surface. The liposomes that are formed using embodiments of the present invention are stabilized by the phospholipids, in addition to their small and relatively uniform particle size, as described in more detail herein. Various molecules from those having a low molecular weight, such as glucose, to those having a high molecular weight, such as peptides and proteins, may be incorporated in liposomes. As mentioned water soluble compounds/drugs are present in aqueous compartments while lipid soluble compounds/drugs and amphiphilic compounds/drugs insert themselves in phospholipid bilayers. The liposomes containing drugs may be administered by various routes, including intravenous, oral inhalation, local application, ocular, etc. Because of this, liposomes can be used for the treatment of many diseases.

Typically multilamellar liposomes (MLV) range from 500 to 10,000 nm, while unilamellar liposomes may be small (SUV) or large (LUV). SUV liposomes are typically smaller than 50 nm, while LUV liposomes are usually larger than 50 nm. Liposomes that are very large are called giant liposomes, whose size may range from 10,000 to 100,000 nm. These may be either unilamellar or multilamellar. The liposomes containing encapsulated

vesicles are called multi-vesicular, and their size may range from 2,000 to 40,000 nm. An exemplary technique of hicrofluidization/microemulsification/homogenization for the large scale manufacture of liposomes is by recycling the sample to reduce the size range. This process is reproducible and yields liposomes with good aqueous phase encapsulation.

Additionally, due to their amphiphilic character, liposomes are a powerful solubilizing system for a wide range of compounds. In addition to these physico-chemical properties, liposomes exhibit many special biological characteristics, including specific interactions with biological membranes and various cells. These properties point to several possible applications with liposomes as the solubilizers for difficult-to-dissolve substances, dispersants, sustained release systems, delivery systems for the encapsulated substances, stabilizers, protective agents, microencapsulation systems and microreactors, to name just a few. Liposomes can be made entirely from naturally occurring substances and are therefore nontoxic, biodegradable and non immunogenic.

The industrial applications include liposomes as drug delivery vehicles in medicine, adjuvants in vaccination, signal enhancers/carriers in medical diagnostics and analytical biochemistry, solubilizers for various ingredients, as well as support matrix for various ingredients and penetration enhancer in cosmetics.

Phospholipids, generally, are lipids that contain one or more phosphate groups. Phospholipids are fatlike organic compounds that resemble triglycerides, but have a fatty acid with a phosphate-containing polar group. The polar end of the molecule is hydrophilic, or soluble in water, and the other end, or the fatty-acid end is hydrophobic, or soluble in fats. Phospholipids are ideal compounds for forming the biological membrane. There are two recognized classes of phospholipids, including phosphoglycerids, or those that have a glycerol backbone, and those phospholipids that contain sphingosine. The most abundant types of phosphoglycerids are phosphatidylcholine (lecithin), phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, and cardiolipin.

Many types of phospholipids may be used in embodiments of the present invention. In one embodiment, the phospholipids used in the composition include one or more of phosphatidylcholine, lysophosphotidylcholine, hydrogenated phospholipids, and unsaturated phospholipids. As mentioned, there are two categories of phospholipids. Examples of phosphoglycerids include phosphatidic acid (phosphatidate) (PA), phosphatidylethanolamine (cephalin) (PE), phosphatidylcholine (lecithin) (PC),

Phosphatidylserine (PS), and Phosphoinositides, which further include phosphatidylinositol (PI), phosphatidylinositol phosphate (PIP), phosphatidylinositol bisphosphate (PIP2), and phosphatidylinositol triphosphate (PIP3). Phospholipids that contain sphingosine, also termed phosphosphingolipids, include ceramide phosphorylcholine (sphingomyelin) (SPH), ceramide phosphorylethanolamine (sphingomyelin) (Cer-PE), and ceramide phosphorylglycereol. The term 'lysophospholipids' (LPL) refers to any phospholipid that is missing one of its two O-acyl chains. Thus, LPLs have a free alcohol in either the sn-1 or sn-2 position. The prefix 'lyso-' comes from the fact that lysophospholipids were originally found to be hemolytic, but is now used to refer generally to phospholipids missing an acyl chain. LPLs are usually the result of phospholipase A-type enzymatic activity on regular phospholipids, such as phosphatidylcholine or phosphatidic acid, although they can also be formed by the acylation of glycerophospholipids or the phosphorylation of monoacylglycerols.

For exemplary purposes only, lysophosphatidylcholine (LPC) has been found to penetrate into the dermis faster than phosphatidylcholine, such that a small amount of LPC can penetrate the skin without damaging skin structure, and is enzymatically degraded into several lipids. LPC has bactericidal and antiviral activity, and as such is a useful agent for dermatological use. LPC also does not damage the structure of the skin. Even further, LPC has been found to have a positive effect on the basement membrane, as it stimulates the synthesis of Laminin 5, a factor supporting the regeneration of an aging basement membrane. Lysophospholipids (LP), such as lysophosphatidic acid and sphingosine 1-phosphate are membrane-derived bioactive lipid mediators. LPs can effect fundamental cellular functions, which include proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. These functions influence many biological processes that include neurogenesis, angiogenesis, wound healing, immunity, and carcinogenesis.

Phospholipids may further include 1,2-Didecanoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dierucoyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Dierucoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dierucoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1,2-Dierucoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Dilinoleoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dilauroyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Dilauroyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dilauroyl-sn-glycero-3-phosphoethanolamine

(Phosphatidylethanolamine), 1,2-Dilauroyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Dilauroyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt) (Phosphatidylglycerol), 1,2-Dilauroyl-sn-glycero-3-phosphoserine (Sodium Salt) (Phosphatidylserine), 1,2-Dimyristoyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1,2-Dimyristoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Dimyristoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt) (Phosphatidylglycerol), 1,2-Dimyristoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium/Ammonium Salt) (Phosphatidylglycerol), 1,2-Dimyristoyl-sn-glycero-3-phosphoserine (Sodium Salt) (Phosphatidylserine), 1,2-Dioleoyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Dioleoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1,2-Dioleoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Dioleoyl-sn-glycero-3-phosphoserine (Sodium Salt) (Phosphatidylserine), 1,2-Dipalmitoyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1,2-Dipalmitoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Dipalmitoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt) (Phosphatidylglycerol), 1,2-Dipalmitoyl-sn-glycero-3-phosphoserine (Sodium Salt) (Phosphatidylserine), 1,2-Distearoyl-sn-glycero-3-phosphate (Sodium Salt) (Phosphatidic acid), 1,2-Distearoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1,2-Distearoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Sodium Salt) (Phosphatidylglycerol), 1,2-Distearoyl-sn-glycero-3[Phospho-rac-(1-glycerol...) (Ammonium Salt) (Phosphatidylglycerol), 1,2-Distearoyl-sn-glycero-3-phosphoserine (Sodium Salt) (Phosphatidylserine), Egg-PC (Phosphatidylcholine), Hydrogenated Egg PC (Phosphatidylcholine), High purity Hydrogenated Soy PC (Phosphatidylcholine), Hydrogenated Soy PC (Phosphatidylcholine), 1-Myristoyl-sn-glycero-3-phosphocholine (Lysophosphatidylcholine), 1-Palmitoyl-sn-glycero-3-phosphocholine (Lysophosphatidylcholine), 1-Stearoyl-sn-glycero-3-phosphocholine (Lysophosphatidylcholine), 1-Myristoyl-2-palmitoyl-sn-glycero 3-phosphocholine (Phosphatidylcholine), 1-Myristoyl-2-stearoyl-sn-glycero-3–phosphocholine

(Phosphatidylcholine), 1-Palmitoyl-2-myristoyl-sn-glycero-3–phosphocholine (Phosphatidylcholine), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), 1-Palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (Phosphatidylethanolamine), 1-Palmitoyl-2-oleoyl-sn-glycero-3[Phospho-rac-(1-glycerol)...] (Sodium Salt) (Phosphatidylglycerol), 1-Palmitoyl-2-stearoyl-sn-glycero-3–phosphocholine (Phosphatidylcholine), 1-Stearoyl-2-myristoyl-sn-glycero-3–phosphocholine (Phosphatidylcholine), 1-Stearoyl-2-oleoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine), and 1-Stearoyl-2-palmitoyl-sn-glycero-3-phosphocholine (Phosphatidylcholine). These examples of phospholipids are provided for exemplary purposes only, and other phospholipids not specifically mentioned herein are contemplated to be included in embodiments of the present invention.

Another component present in the composition described herein is oils that are rich sources of essential fatty acids, behenic acid, and oleic acid. During life, skin is subjected to different perturbations (e.g., puberty, pregnancy, menopause, disease) and aggressions (e.g., UV, pollution, cold, detergent). These upheavals and external aggressions induce a decrease of membrane fluidity involving a disruption of the lipidic barrier (e.g., cutaneous dryness and roughness) and a loss of the epidermic elasticity (e.g., formation of irregularities, stretch marks, and furrows). All of these events induce a cutaneous dehydration accompanied b y the appearance of squamas and wrinkles on the skin's surface. The supply of essential fatty acids and antioxidant molecules can restore the cutaneous permeability and the function of the skin barrier. They also contribute to the control of the imperceptible water loss and maintain moisture of the skin.

Behenic acid and oleic acid, when used by themselves, may be irritating when applied to the skin, which makes them difficult to use as permeation enhancers. While having an irritating effect on the skin, these acids are also effective vehicles at delivering drugs through the skin. In one embodiment, an oil from a tree in Brazil has the highest natural sources of behenic acid and oleic acid. The tree is called Pentaclethara Macroloba, or more commonly termed the Pracaxi tree. Pentaclethra Macroloba seed oil, also called Pracaxi oil, is extracted from the tree, and as mentioned, contains high concentrations of behenic acid and oleic acid. Pracaxi oil has been used by people living near the Amazon river as an antioxidant, and has been thought to have antifungal and antibacterial properties. Further, Pracaxi oil has been widely used to treat snake bites and aid in the healing of ulcers. Pracaxi oil, however, has not been used as a permeation enhancer. Typically, Pracaxi oil

contains about 20% behenic acid and about 35% oleic acid. In some cases, it may contain more than these percentages. As the behemic acid and oleic acid are present in an oil, the effects of the acids are less irritating on the skin, and as such makes the oil a good choice for one of the ingredients of a penetration enhancer.

Another oil that may be used in some embodiments in combination with Pracaxi oil is Plukenetia Volubilis seed oil, also known as Inca Inchi. This oil is native to the Amazon Rainforest. The seeds of Inchi are high in protein (around 27%) and oil (around 35 - 60%) content. This oil extracted from the Plukenetia volubilis plant is one of the largest plant sources of the Omega family of fatty acids, including a high concentration of protein. The oil is also rich in iodine and vitamin A and vitamin E. This is a natural oil with an exceptional content in polyunsaturated fatty acids (greater than 90%) and tocopherols (1.5 to 2 g/kg). It is a vegetable oil having both essential fatty acids in such a high amount, including 49% of alphalinolenic acid (omega-3) and 34% of linoleic acid (omega-6). While Plukenetia Volubilis seed oil has a very high amount of fatty acids, it also has high amounts of behenic acid (10-30%) and oleic acid (35-80%).

As mentioned, behenic acid and oleic acid, when used by themselves, can be very rough on a person's skin. But, when an oil such as Plukenetia Volubilis seed oil and/or Pracaxi oil are used, they work to enhance the restoration of cutaneous barrier organization and epidermal elasticity, in addition to contributing to the control of imperceptible water loss, thus maintaining skin hydration. This is, at least in part, due to the high amounts of essential fatty acids in these oils. The link between skin permeation and hydration is clear. Increasing the permeability of the stratum corneum may be achieved by the increase of water content in this tissue. Hydration by occlusion may cause a swelling of the corneocytes and subsequently may increase the skin permeation of actives. Here, the utilization of physiological lipids, essential fatty acids, and phospholipids provide penetration power with restorative benefits to the skin.

Another component of the composition described herein is skin lipids. Skin lipids, as used herein, are those lipids that are present at the skin's surface. Examples of skin lipids that may be used in the composition described herein include ceramides and/or squalene. Ceramides are the major lipid constituent of lamellar sheets Ceramides are a structurally heterogeneous and complex group of sphingolipids containing derivatives of sphingosine bases in amide linkage with a variety of fatty acids. Differences in chain length, type, and extent of hydroxylation and saturation are responsible for the heterogeneity of the

epidermal sphingolipids. Ceramides play an important role in structuring and maintaining the water permeability barrier function of the skin. In conjunction with the other stratum corneum lipids, they form ordered structures. A structured semi-occlusive barrier that increases skin hydration is a positive influence on the penetration of active ingredients.

Another skin lipid that may be used is squalene, which is a lipid fat in the skin. When used together with a ceramide and a phospholipid, such as phosphatidylcholine, the formulation is mild such that is can be used on even sensitive skin. Squalene also helps to decrease water evaporation, thus speeding up skin permeation of actives and decreasing irritation made by surfactants found in emulsions. Squalene, being a natural emollient, imparts an elegant feel to formulations in which it is used. It is excellent for use in skin care and helps skin to retain moisture and feel soft and conditioned without feeling greasy.

Yet another component of the composition described herein is butters rich in linoleic acid and linolenic acid. One example of this type of butter is butyrospermum parkii butter, also known as shea butter. Other exemplary butters that may be used in embodiments of the present invention include, but are not limited to, cupuacu butter, buriti butter, passionfruit butter, mango butter, tucuma butter, palm butter, murumu butter, chamomile butter, cocoa butter, orange butter, lemon grass butter, avocado butter, tamanu butter, aloe butter, shea butter, monoi butter, pomegranate butter, almond butter, jojoba butter, red palm butter, acai butter, olive butter, matcha green tea butter, brazil nut butter, macadamia butter, kokum butter, mafura butter, coffee butter, tucuma butter, ucuuba butter, bacuri butter, and chamomile butter.

In embodiments of the present invention, the use of behenic acid, oleic acid, phospholipids, and the omega family enhance the permeation of drugs or other active ingredients through the skin in-vitro and in-vivo.

As mentioned, the composition described herein is produced such that the size of the particles is in the range of 5-20 microns, which provides a more stable vesicle than if the particle sizes were larger. Various methods may be used to produce particle sizes of about 5-20 microns. In one embodiment, a high pressure homogenizer is used. Using a high pressure homogenizer, the composition would be put under extreme pressure and forced through a very small opening. It is cycled through a number of times to achieve the desired particle size. But preferably, a high shear homogenizer is used in embodiments of the present invention, such as a high shear rotor-stator homogenizer under negative pressure. In one embodiment, an IKA Master Plant homogenizer is used, which can achieve RPMs over

8,000. Using this preferred method, the desired particle size is achieved without the use of a high pressure homogenizer, which is generally more expensive to use than the high shear homogenizer.

While concentrations of the components described herein may vary, table 1 below illustrates exemplary concentrations, including the four main components described above, a concentration range, and optimal concentrations for each of the four components.

Table 1. Exemplary concentrations of the components

Ingredients	Range concentration	Optimal concentration
Phospholipids	0.05-5%	2%
Oils	1-20%	3%
Skin Lipids	0.1-3%	0.5%
Butters	1-10%	2%

In one embodiment, the formulation contains about: 5-40% w/w Phosal 75 SA (alcohol; purified phosphatidylcholine; safflower oil; glyceryl stearate; coconut oil, ascorbyl palmitate); 5-40% w/w DMS 3015 (water, alcohol, caprylic/capric triglyceride, hydrogenated lecithin, butyrospermum parkii butter, squalene, and ceramide 3); 5-20% w/w Lipactive Inca Inchi (plukenetia volubilis seed oil, tocopherol); 5-40% w/w Pracaxi oil; and 10-90% w/w Purified water.

Example 1

In order to test particle size of the composition, a particle size analysis was conducted on a Malvern MasterSizer diffractor. When the composition was produced, 90% of the solution had a particle size of around 9 microns. This is clearly shown in FIG. 1. FIG. 1 is a logarithmic graph 100 that illustrates the particle size distribution, and shows volume, in percent, on the "y" axis and the particle size in microns (μm) on the "x" axis. As mentioned, while compositions used for permeation enhancements are typically more in the range of 10-100 microns, the liposomes of the composition described herein are in the range of 5-20 microns. In some embodiments, a small percentage of the liposomes have particle sizes greater than 20 microns, but still less than 100 microns, or even 80 microns. FIG. 2 is a microscopy picture 200 of the lipoderm core showing the distribution of liposome particle sizes.

Example 2

While there are various methods to produce the composition disclosed herein, such as the embodiment listed above, not all of these methods will be disclosed herein for the

sake of brevity. For exemplary purposes only, the penetration enhancement composition may be produced in the amount of 500 gm. Initially, Pracaxi oil is added to a vessel, along with Plukenetia volubilis seed oil and Phosal 75 SA, whose components are listed above. If Phosal 75 SA is not used, its components may be individually added to the vessel. The mixture of these components is headed to about 60°C, with slow mixing at a mixing speed of around 500 RPM. The heat is then stopped and the mixing speed is increased to 1000 RPM. In another vessel, water and DMS 3015, whose components are listed above, are mixed until congealed. The contents of the two vessels are mixed together and mixed at a mixing speed of about 4000 RPM for approximately two minutes. The mixing is then stopped such that the composition can be packaged in the appropriate containers.

Example 3

Another example is provided to produce about 100 kg of the penetration enhancement composition using a high pressure production method. Here, water and DMS 3015 are added to a first vessel. These components are mixed in the first vessel at a mixing speed of about 5000 RPM for about five minutes. In a second vessel, Pracaxi oil, Plukenetia volubilis seed oil, and Phosal 75 SA are mixed together until there is a clear solution. After about five minutes of mixing, the mixing is stopped. The mixture in the second vessel is added to the mixture in the first vessel. These are mixed together for about ten minutes at a mixing speed of about 5000 RPM. Using a vacuum system, the pressure is decreased to about negative 2.5 bars for about five minutes. Air is discarded from the vacuum and the composition is pumped out using the dispersing outlet of the vessel.

Example 4

In order to illustrate the ability of the composition described herein to function as a permeation enhancer, in-vitro ex-vivo (human skin) testing was performed using the Franz diffusion cell method. The active ingredient, here a drug, is ketoprofen, a commonly used non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It generally acts by inhibiting the body's production of prostaglandin. Ketoprofem may be offered as a gel for topical application. When tested, the concentration of the permeation enhancement composition was about 5% w/w. The concentration of the ketoprofen used in the study was about 10% w/w. Table 2 below illustrates the various other components of the composition, other than ketoprofen.

Table 2. Components of composition when used with an active ingredient, ketoprofen

PHASE A	% w/w
Phenoxyethanol	0.55
Glycerin USP	2
Purified Water	68
Edetate Disodium Dihydrate	0.2
PHASE B	
Stearyl Alcohol NF	2
Cetearyl Alcohol and Ceteareth-20	4.5
Dow Corning 200 (350 CST) (Dimethicone)	1
Isopropyl Myristate NF	5.5
Cetyl Alcohol	2.3
Butylated hydroxytoluene (BHT)	0.25
Wheat Germ oil 2.0 Iu/G min	3
Magnesium Aluminium Silicate NF	0.035
Xanthan Gum	0.035
Caprylic/Capric Triglycerides	1
PHASE C	
The Composition	5
Purified water	5
PHASE D	
SEPIGEL 305 (Polyacrylamide/C13-14 Isoparaffin/Laureth-7)	1
PHASE E	
Methylchloroisothiazolinone / Methylisothiazolinone	0.035
Purified water	1

In FIG. 3, is a graph 300 that illustrates the percutaneous flux rate results. The mean flux in $\mu g/cm^2$/hour is shown on the "y" axis and the mid time in hours is shown on the "x" axis. The illustrated line represents the formulation with 5% of the composition being the permeation enhancer. As shown, the flux is highest at around 2 hours. Steady-state flux (mass/time or mass/area/time) is determined from the slope of the linear portion of the cumulative chemical absorbed versus the time plot. Comparing these fluxes across a range of pharmaceutical products with exactly the same method allows acceptable rank-ordering of

compounds for their ability to penetrate skin, which can be useful for selection of compounds or development of formulations.

FIG. 4 is a graph 400 that illustrates the amount (in percent) of permeation of ketoprofen through human skin when using the permeation enhancement composition described herein. About 24.6% is absorbed into the skin when using the permeation enhancement composition.

FIG. 5 illustrates a flow diagram of a method 500 for preparing a natural composition to be used for skin permeation, in accordance with an embodiment of the present invention. At step 510, various components are combined to form a natural composition. These components include one or more phospholipids, one or more oils having essential fatty acids, behenic acid, and oleic acid, one or more skin lipids, and a butter having linoleic acid and linolenic acid. One of the oils, in one embodiment, is Pracaxi oil. At step 512, the composition is dispersed in a vessel using a high shear homogenizer. The composition may be mixed in different batches and then all bathes may be mixed together. Mixing rates may vary, and may include speeds of 1000 RPM, 5000 RPM, etc. As mentioned, a high shear homogenizer may be used for the dispersing of the composition. At step 514, negative pressure is created in the vessel having the composition. In one embodiment, the pressure reaches about negative 2.5 bars, although this pressure may vary. The negative pressure, in one embodiment, is created by a vacuum system. The methods presented herein may allow for the size of the liposomes to reach the range of 5-20 microns, which allows for more stable particles and better skin permeation than larger particle sizes.

The present invention has been described in relation to particular embodiments, which are intended in all respects to be illustrative rather than restrictive. Since many possible embodiments may be made of the invention without departing from the scope thereof, it is to be understood that all matter herein set forth is to be interpreted as illustrative and not in a limiting sense. Alternative embodiments will become apparent to those of ordinary skill in the art to which the present invention pertains without departing from its scope.

From the foregoing, it will be seen that this invention is one well adapted to attain all the ends and objects set forth above. It will be understood that certain features and subcombinations are of utility and may be employed without reference to other features and subcombinations. This is contemplated and within the scope of the claims.

CLAIMS

What is claimed is:

1. A method for producing liposomes in a composition for skin permeation, the liposomes having a small particle size, the method comprising: providing the composition comprising water, one or more skin lipids, one or more butters having linoleic acid and linolenic acid, Pracaxi oil, Plukenetia Volubilis Seed oil, and one or more phospholipids; in a vessel, dispersing the composition utilizing a high shear homogenizer; and creating negative pressure in the vessel to produce a final composition, wherein liposomes are produced and are present in the final composition, and wherein the liposomes have particle sizes of around 5-20 microns to improve skin permeation of an active ingredient formulation to which the final composition is added.

2. The method of claim 1, wherein the negative pressure is created by a vacuum system.

3. The method of claim 2, wherein the vacuum system decreased the pressure to about negative 2.5 bars.

4. The method of claim 1, further comprising adding the composition to a topical formulation such that permeation is enhanced of one or more active ingredients in the topical formulation.

5. A natural composition used for skin permeation, the composition comprising a combination of: one or more phospholipids; Pracaxi oil; one or more skin lipids; and a butter having linoleic acid and linolenic acid, wherein when components of the composition are combined, liposomes are produced in the composition having particle sizes around 5-20 microns such that skin permeation is increased by way of small particle sizes.

6. The natural composition of claim 5, wherein the natural composition is used as a lamellar gel phase promoter.

7. The natural composition of claim 5, wherein the natural composition is a liquid or a semi-liquid.

8. The natural composition of claim 5, wherein the Pracaxi oil contains behenic acid and oleic acid such that the composition is less irritating to skin than the behenic acid and the oleic acid used alone without the Pracaxi oil.

9. The natural composition of claim 5, wherein the one or more phospholipids include an unsaturated phospholipid, lysophosphotidylcholine, and hydrogenated phospholipid.

10. The natural composition of claim 5, wherein the particle sizes of around 5-20 microns allows for increased skin permeation of an active ingredient added to the natural composition.

11. The natural composition of claim 8, wherein the Pracaxi oil forms a pseudo-barrier formation on skin to delay an interaction of behenic acid and oleic acid with the skin.

12. The natural composition of claim 5, wherein the one or more skin lipids are one or more of ceramide or squalene.

13. The natural composition of claim 5, wherein the butter is Butyrospermum Parkii butter.

14. The natural composition of claim 5, wherein the one or more phospholipids are responsible for the creation of the liposomes in the natural composition.

15. The natural composition of claim 5, wherein the Pracaxi oil contains high amounts of essential fatty acids such that imperceptible water loss is controlled and skin hydration is maintained.

16. A method for producing liposomes in a composition used for skin permeation, the method comprising: providing a natural composition, the natural composition comprising, one or more phospholipids, and one or more oils having essential fatty acids, behenic acid, and oleic acid, wherein one of the one or more oils is Pracaxi oil; combining the one or more phospholipids and the one or more oils; in a vessel, dispersing the composition at speeds up to 5,000 rotations per minute (RPM); and creating negative pressure in the vessel to produce liposomes having particle sizes around 5-20 microns.

17. The method of claim 16, wherein a vacuum system is used to create the negative pressure to about negative 2.5 bars.

18. The method of claim 16, further comprising adding the composition to a topical formulation such that permeation is enhanced of one or more active ingredients in the topical formulation.

19. The method of claim 18, wherein the particle sizes of the liposomes allow for increased skin permeation of the one or more active ingredients in the topical formulation.

20. The method of claim 18, further comprising contacting the topical formulation that includes the composition with skin surface.

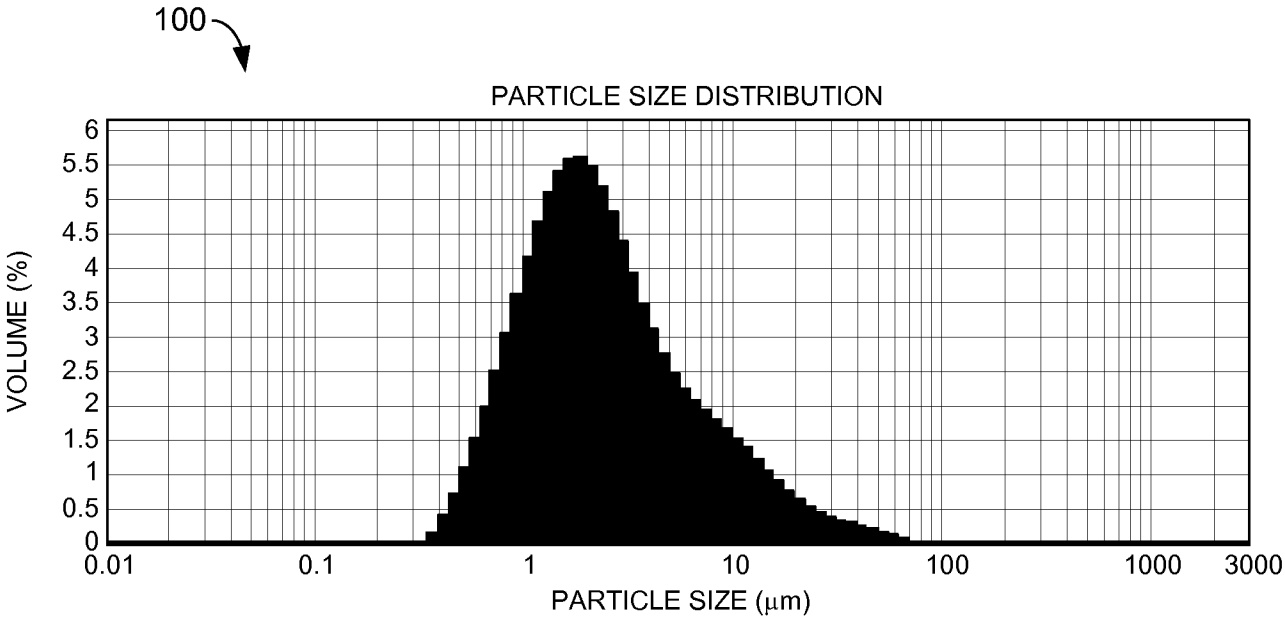

100
PARTICLE SIZE DISTRIBUTION
VOLUME (%)
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0.01
0.1
1
10
100
1000
3000
PARTICLE SIZE (μm)

FIG. 1.

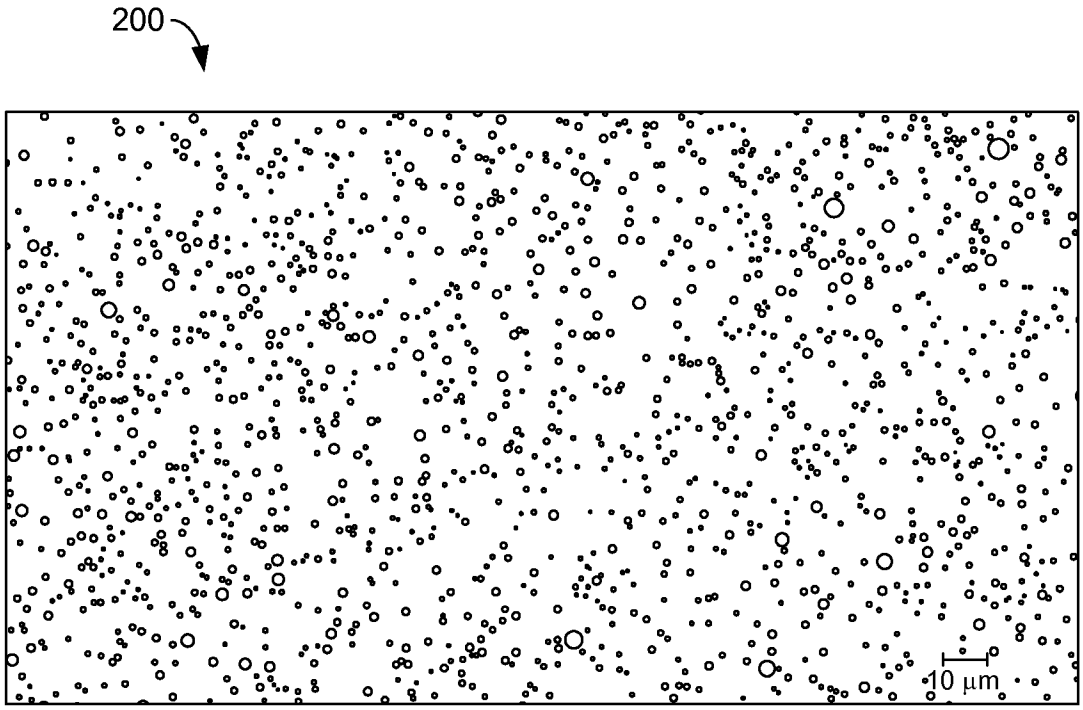

200
10 μm

FIG. 2.

300

MEAN FLUX (μm/CM2/HR) RESULTS: ACROSS DONOR SUMMARY
PERCUTANEOUS ABSORPTION OF KETOPROFEN THROUGH EX-VIVO
HUMAN TRUNK SKIN OVER 48 HOURS FROM A SINGLE APPLICATION

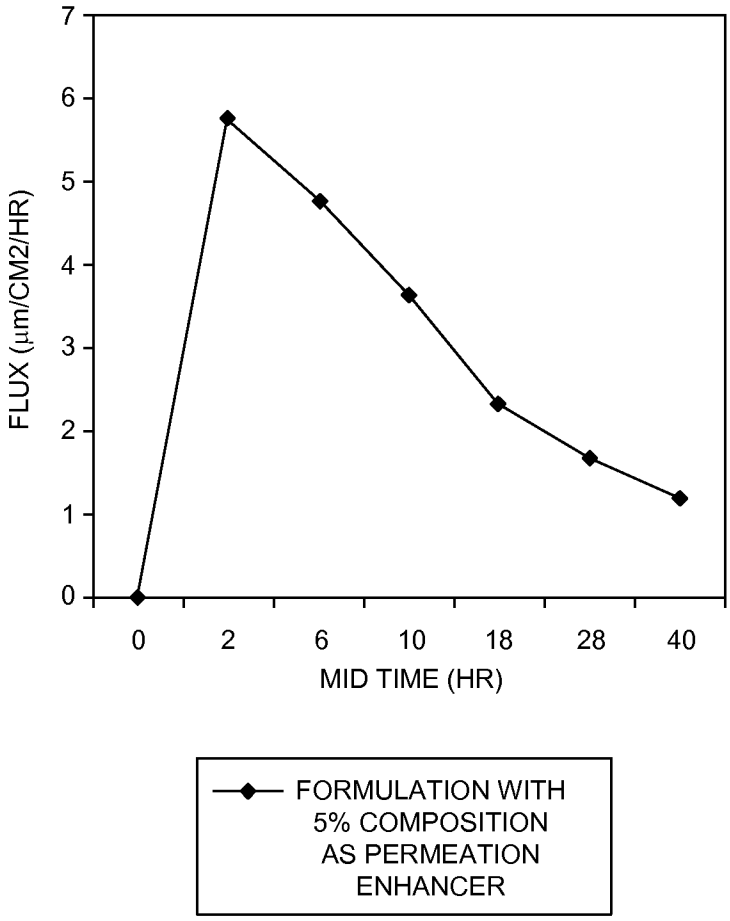


FIG. 3.

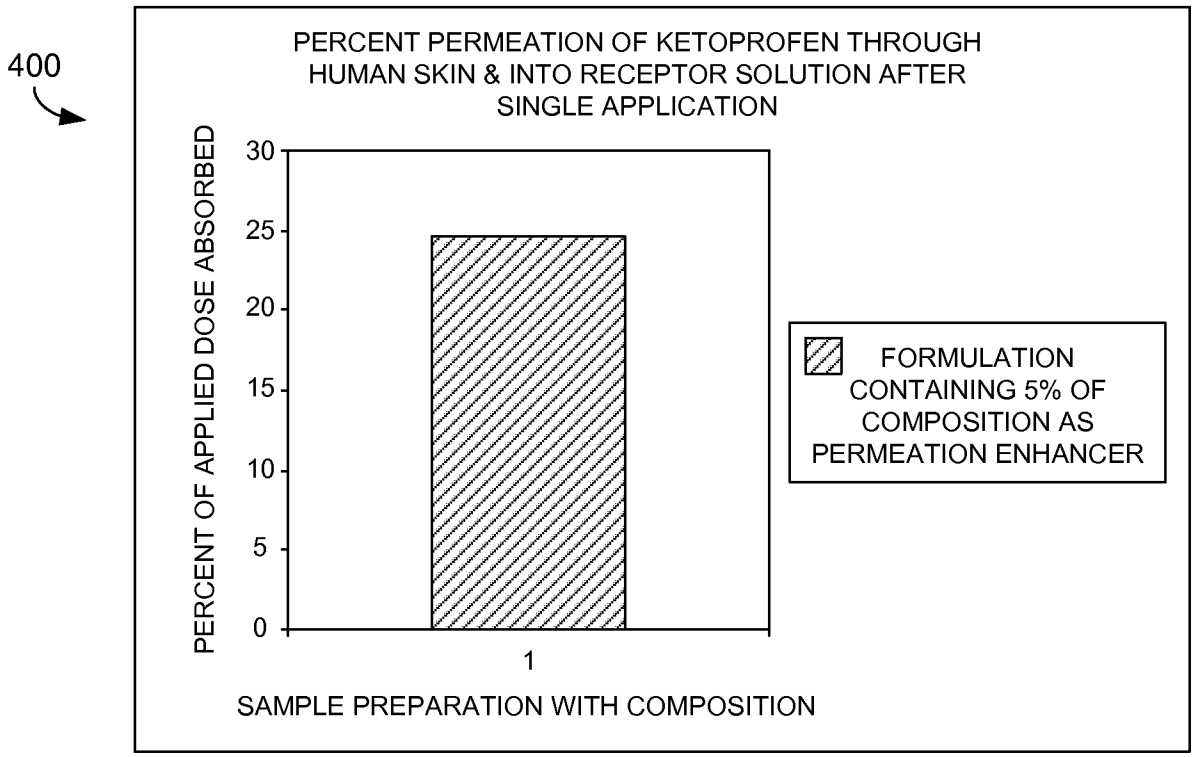

400
PERCENT PERMEATION OF KETOPROFEN THROUGH HUMAN SKIN & INTO RECEPTOR SOLUTION AFTER SINGLE APPLICATION
PERCENT OF APPLIED DOSE ABSORBED
30
25
20
15
10
5
0
1
SAMPLE PREPARATION WITH COMPOSITION
FORMULATION CONTAINING 5% OF COMPOSITION AS PERMEATION ENHANCER

FIG. 4.

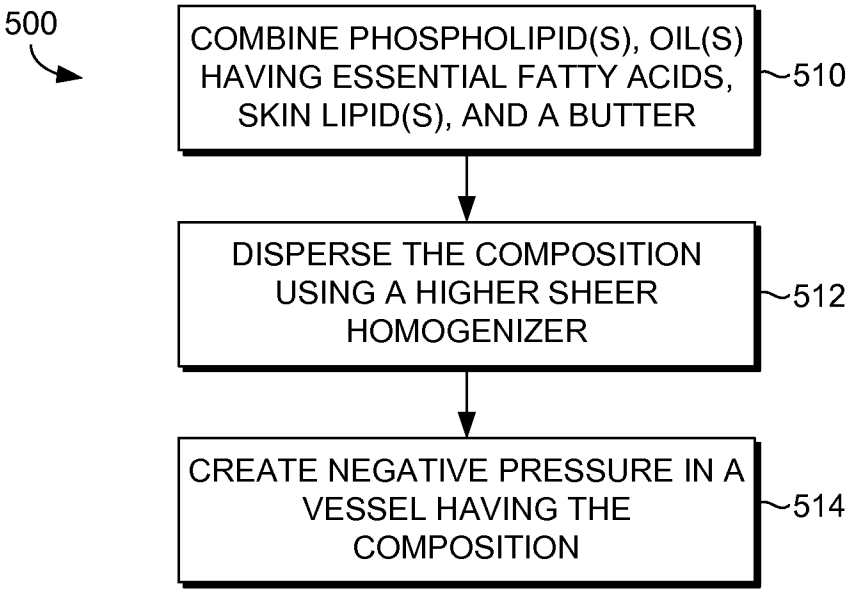

500
COMBINE PHOSPHOLIPID(S), OIL(S) HAVING ESSENTIAL FATTY ACIDS, SKIN LIPID(S), AND A BUTTER
510
DISPERSE THE COMPOSITION USING A HIGHER SHEER HOMOGENIZER
512
CREATE NEGATIVE PRESSURE IN A VESSEL HAVING THE COMPOSITION
514

FIG. 5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/23992

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/127 (2012.01)
USPC - 424/450
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 9/127 (2012.01)
USPC: 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): A01N 65/00,25/00 (2012.01)
USPC: 424/725; 514/783, 785, 786, 943, 946, 947, 975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB), Dialog
Liposome, water, lipid ceramide, squalene, butter (Butyrospermum Parkii butter or shea butter), linoleic acid, linolenic acid, pracaxi oil , (Butyrospermum Parkii butter or shea butter), linoleic acid, linolenic acid, pracaxi oil barrier, behenic acid, oleic acid, plukenetia etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0196895 A1 (GOLZ-BERNER et al.) 6 August 2009 (06.08.2009) Abstract, para[0007], para[0009], para[0010], para[0011], para[0021], para[0022], para[0038], para[0039], para[0052], para[0060]	1-20
Y	US 2003/0017183 A1 (POLLOCK) 23 January 2003 (23.01.2003) para[0009], para[0013], para[0014], para[0034], para[0035]	1-20
Y	US 2009/0285876 A1 (HEIN et al.) 19 November 2009 (19.11.2009) para[0033]	1-20
Y	US 5,505,960 A (LUCCHETTI et al.) 9 April 1996 (09.04.1996) Abstract, col 5, ln 30-37	1-4 and 16-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2012 (06.05.2012)	23 MAY 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)