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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to a lipid layer forming composition optionally comprising a pharmacologically or cosmetically active agent or a protective agent for administration onto a surface of a living organism, in particular onto a membrane, such as the skin or a mucous membrane. The present invention also relates to a method of forming a lipid layer on a surface. The present invention furthermore relates to a layer capable of carrying a biologically active agent disposed on a surface of a living organism or a tissue or organ thereof and to a surface covered with such a lipid layer.

BACKGROUND OF THE INVENTION

[0002] In the pharmaceutical and cosmetic fields there is a need of a lipid composition capable of incorporating lipids and pharmacologically or cosmetically active compounds and of being evenly applicable to biological surfaces, in particular in form of a thin coherent layer. The lipid composition should be of low viscosity to facilitate delivery, in particular by spraying. While the viscosity of such a composition can be substantially reduced by adding a volatile solvent, the initially formed unstable coherent layer comprising lipid, pharmacologically or cosmetically active agent and solvent should change to a stable coherent layer by evaporation of the solvent within a time period as short as possible.

[0003] While a high solvent content is beneficial by reducing viscosity it requires more time for evaporation. In other words, a high solvent content in a lipid composition of the aforementioned kind extends the time period during which the applied composition is comparatively unstable. By "comparatively unstable" is understood the stability of an applied composition comprising substantial amounts of solvent in respect of the stability of the same composition after evaporation of all or substantially all solvent. Examples of such compositions include compositions for topical administration of pharmaceutically active compounds and compositions for skin care. Compositions rich in lipids are prone to form liquid crystals, a formation which is accompanied by high viscosity caused by high degree of local order.

[0004] WO 01/87344 A1 discloses a pharmaceutical or cosmetic composition comprising one or more pharmaceutically or cosmetically active agent, one or more organosilicon compound based on oligomeric or polymeric diorganosiloxane, and one or more phospholipid. When applied to the skin, the composition of WO 01/87344 A1 penetrates directly within a short period of time into the skin or into the external layers of plants treated with it, so that it cannot be rubbed off since it is rapidly absorbed into the interior of the body. For embodiments intended to be used topically in humans or animals the organosilicon compound of the composition has a boiling point varying between 15 °C and 150 °C at ambient pressure.

OBJECTS OF THE INVENTION

[0005] It is an object of the invention to provide a lipid composition for administration onto a surface of a living organism which is easily applicable and capable of forming a coherent stable oily lipid layer on the surface.

[0006] It is another object of the invention to provide such a lipid composition capable of carrying a biologically active agent.

[0007] Still another object of the invention is to provide such a lipid composition that does not cause swelling when applied to the skin.

[0008] A further object of the invention is to provide such a lipid composition that does not cause irritation nor give a burning feeling when applied on the skin.

[0009] Further objects of the invention will be evident from the following summary of the invention, preferred embodiments thereof described in form of examples, a drawing illustrating some of the preferred embodiments, as well as from the appended claims.

SUMMARY OF THE INVENTION

[0010] The present invention is based on the insight that silicone oils of a boiling point of 180 °C or higher, in particular of a boiling point of 200 °C or higher, can be used as an evaporating component of lipid carrier compositions for topical application, the compositions additionally comprising polar lipid and lower alcohol. "Evaporating component" indicates the capacity of silicone oils to evaporate, in spite of their high boiling point, within a short time upon application of the composition to the skin or other surface at ambient temperature or at a higher temperature. By their evaporation and the evaporation of the lower alcohol a layer of polar lipid is formed on the skin or other surface.

[0011] According to the present invention is provided a lipid layer forming carrier composition of the aforementioned kind, comprising volatile silicone oil, from 10 % by weight to 30 % by weight of phospholipid, from 10 % by weight to 30 % by weight of ethanol, optionally water in an amount of 5 % by weight or less, wherein the silicone oil has a boiling point above 180°C, in particular above 200°C, and wherein the silicone oil has a heat of vaporization (kJ/kg) at 25 °C of from about 100 kJ/kg to about 300 kJ/kg, with the proviso that the content of volatile silicone oil is 50 % by weight or more. The lipid carrier composition of the invention is useful for providing a stable coherent polar lipid layer on a surface of a living organism.

[0012] By incorporation of a pharmacologically or cosmetically active agent or a protective agent the lipid carrier composition of the invention is transformed to a pharmaceutical or cosmetic lipid composition of the invention or a protective lipid composition of the invention. The pharmaceutical, cosmetic or protective lipid composition of the invention comprising an active agent of the aforementioned kind can be used for delivering the agent on a surface of a living organism on which it is applied. A preferred surface is the skin or a mucous membrane such as the nasal or gastric mucous membrane. Another preferred surface is a plant surface, such as the surface of a grain or seed.

[0013] The present invention is based on the finding that a particular class of solvents, volatile silicone oils, optionally in combination with a lower aliphatic alcohol, are particularly useful in formulating a lipid

carrier composition comprising a polar lipid. After application onto a biological surface the lipid carrier composition of the invention forms an unstable polar lipid layer from which the volatile silicone oil and, if present, the lower aliphatic alcohol, evaporates readily, leaving a stable lipid layer substantially consisting of polar lipid. Correspondingly, a stable polar lipid layer comprising a pharmaceutically or cosmetically active agent is formed by incorporating the active agent into the lipid carrier composition of the invention, applying it to a biological surface, and allowing the solvent or combination of solvents to evaporate. The low viscosity of the carrier composition of the invention and the pharmaceutical or cosmetic composition of the invention seems to be due to the inability of polar lipids to form lyotropic liquid crystals, such as lamellar, hexagonal and various cubic phases of high viscosity. The lipid carrier composition and the pharmaceutical or cosmetic composition of the invention are clear and of low viscosity even at concentrations of polar lipid as high as 20 % by weight.

[0014] In contrast, polar lipid compositions corresponding to those of the invention but in which the silicone oil component is substituted by a corresponding amount of water are slightly viscous dispersions at low polar lipid concentrations or thick gels at higher polar lipid concentration tested, for instance 20 % by weight of the composition. The high viscosity of the latter composition does not allow administration by spraying. By using the volatile silicone oil as the diluent instead of water, it is possible to incorporate a surprisingly high amount of polar lipid while only insignificantly affecting viscosity.

[0015] Silicone oils of personal care grade or pharmaceutical grade useful in the invention are known in the art. Examples of useful silicone oils include dekamethylcyclopentasiloxane [Dow Corning(R) 245 Fluid] and dodekamethylcyclohexasiloxane (Dow Corning (R) 246 Fluid). While pentasiloxanes and hexasiloxanes are preferred, hepta- and octasiloxanes are also potentially useful. The silicone oils may be cyclic siloxanes, that is, cyclomethicones, or linear siloxanes, that is, dimethicones. The silicone oils of the invention can be used in pure form or in admixture. While permethyl substitution is preferred, one or more methyl groups of a siloxane can be substituted by lower alkyl, in particular by ethyl, propyl or isopropyl. Siloxanes partially or fully substituted by lower trifluoroalkyl, in particular trifluoromethyl and pentafluoroethyl, are also useful in the invention.

[0016] In addition to chemical inertness the usefulness of the silicone oil of the invention is determined by its volatility. In spite of its high boiling point above 180 °C, in particular above 200 °C, the silicone oil of the invention evaporates readily due to the low heat of vaporization of this class of compounds. In the invention the silicone oil has a heat of vaporization (kJ/kg) at 25 °C of from about 100 kJ/kg to about 300 kJ/kg, more preferred of from about 120 kJ/kg to about 200 kJ/kg. Even more preferred is a silicone oil having a heat of vaporization of from 140 kJ/kg to about 180 kJ/kg at 25 °C

[0017] The silicone oil of the invention provides the carrier composition and the pharmaceutical or cosmetic composition of the invention with at least the following advantageous features i) the ability to incorporate high contents of polar lipid material; ii) the formation of thermodynamically stable solutions; iii) the low viscosity of the solutions formed making them suitable for, e.g., spraying, dropping, painting or instilling.

[0018] The lower aliphatic alcohol of the invention is ethanol. Other useful alcohols are glycerol and 1,2-propanediol. Solvents other than lower alcohols may also be used, such as dimethyl sulfoxide and N-methyl-2-pyrrolidone. In applications with less stringent biocompatibility requirements solvents such as chloroform, dichloromethane, pyridine, hexane, and methanol can be used.

[0019] The polar lipid of the invention is a phospholipid. A particularly preferred phospholipid is

phosphatidyl choline. Other preferred phospholipids are phosphatidyl ethanolamine and phosphatidyl inositol. A particularly preferred glycolipid is galactolipid. A preferred galactolipid is digalactosyl-1,2-diacylglycerol as such or in admixture with other galactolipids and/or phospholipids and/or sphingolipids.

[0020] Technical scale commercial polar lipids useful in the invention contain substantial amounts of non-polar lipids, so as to be composed of up to about 50 to 60 % by weight of non-polar lipid. Thus, according to a further preferred aspect of the invention, the polar lipid component of the carrier composition or the pharmaceutical or cosmetic composition of the invention comprises a non-polar lipid in an amount of up to 30 % by weight or more, such as up to 50% or 60 % by weight and even up to 75 % by weight. Non-polar lipids as components of polar lipids are preferably mono- and diglycerides and their mixtures, in particular monoglycerides. In a polar lipid of the invention a higher proportion of mono- and diglyceride, in particular of monoglyceride, can be tolerated than one of triglyceride.

[0021] The use of a lower aliphatic alcohol such as absolute ethanol for the dissolution of the oily polar lipid of the invention is particularly useful with a lipid of a low chain-melting temperature. The chain-melting temperature is the temperature at which the acyl chains of a membrane lipid undergo a phase transition in an excess of water, from a solid-like state to a melted or liquid-like state. Membrane lipid materials like Lipoid S75, Lipoid S45, Phospholipon 50, Lipoid S100, and DOPC all have chain-melting temperatures below 0 °C and can thus be readily dissolved in C₂ to C₄ alcohol, in particular ethanol, at concentrations up to 50 % by weight and even higher.

[0022] To produce the carrier composition of the invention the phospholipid, in particular a membrane lipid mixture such as a lecithin or fractionated oat oil, is dissolved in ethanol and then diluted with a volatile silicone oil, resulting in a low-viscous, sprayable, homogenous liquid. A typical example of such a composition is one consisting of 49 % DC 345, 37 % fractionated oat oil (LTP Lipid Technologies Provider AB, Sweden), and 14 % by weight of absolute ethanol. Fractionated oat oil is obtained from crude oat oil and is enriched in polar lipids. It typically contains about 50 % by weight of non-polar lipid, such as triacylglycerol and diacylglycerol, and about 50 % by weight of polar lipid, such as phospholipid and galactolipid. Typically, the content of digalactosyldiacylglycerol in a fractionated oat oils is about 20 % by weight. Suitable fractionated oat oils are disclosed, for instance, in WO 99/44585 A1.

[0023] Lipids like phosphatidyl ethanolamine, for instance dioleoylphosphatidyl ethanolamine (DOPE), or sphingolipid, for instance sphingomyelin, can also be used as a polar lipid of the invention as such or in admixture with other polar lipids. DOPE has a chain-melting temperature of -16 °C in water and can be dissolved in absolute ethanol at 50 % by weight or higher at elevated temperatures (>60 °C). Such solution can be diluted with volatile silicone oil such as DC 345, resulting in a clear, low-viscous liquid.

[0024] Although small amounts of water, such as 1 % or 2 % and even up to about 5 % by weight can be tolerated, the lipid carrier composition of the invention is preferably substantially water-free, in particular has a water content of less than 5 % by weight, preferably of less than 2 % or 1 % by weight and even less than 0.5 % by weight or 0.2 % by weight.

[0025] The pharmacologically or cosmetically active agent or the protective agent can be incorporated in the lipid carrier composition in an amount of from 0 % to 2 % by weight or to 5 % by weight and even up to 25 % by weight or more in respect of total non-volatile components of the carrier composition, in particular polar lipid, remaining upon evaporation of its volatile components.

[0026] The pharmacologically active agent for incorporation into the lipid carrier composition of the invention is preferably selected from the group consisting of: antimicrobial agent, antibiotic; antimycotic agent; antibacterial agent; antifungal agent; antiviral agent; antiseptic; anti-phlogistic; anti-pruritic agent; anti-psoriatic agent; antitussive agent; anti-alopecia agent; anti-acne agent; anti-inflammatory agent; antiulcer agent; local anaesthetic; immune response modifying agent.

[0027] In particular, the pharmacologically active agent of the invention is selected from: antibacterial agents, such as oxytetracycline, fusidic acid, gentamycin, mupirocin, retapamulin (and pharmaceutically acceptable salts and derivatives thereof); antimycotic agents, such as nystatin, clotrimazole, miconazole, econazole, ketoconazole, bifonazole, and combinations of imidazole and triazole derivatives, ciclopirox, terbinafine, fluconazole, and amorolfine (and pharmaceutically acceptable salts and derivatives thereof); antiviral agents, such as aciclovir, valaciclovir, penciclovir, famciclovir, foscarnet (sodium phosphonate hexahydrate) and docosanol (and pharmaceutically acceptable salts and derivatives thereof); antiseptics, such as chlorhexidine and hydrogen peroxide; anti-inflammatory agents (glucocorticoids), such as hydrocortisone, clobetasone, triamcinolone, betamethasone, mometasone, and clobetasol (and pharmaceutically acceptable salts and derivatives thereof); antiphlogistics/analgesics (NSAID's), such as acetylsalicylic acid, diclofenac, and ibuprofen (and pharmaceutically acceptable salts and derivatives thereof); antipruritic agents, such as glucocorticoids, for example, hydrocortisone, clobetasone, and betamethasone, and local anaesthetics, for example, lidocaine and prilocaine (and pharmaceutically acceptable salts and derivatives thereof); antipsoriatic agents, such as calcipotriol and cyclosporine A (and pharmaceutically acceptable salts and derivatives thereof); agents for treatment of eczema and atopic dermatitis: tacrolimus and pimecrolimus (and pharmaceutically acceptable salts and derivatives thereof); antiglaucomatous agents, such as timolol, betaxolol, latanoprost, bimatoprost, and travoprost (and pharmaceutically acceptable salts and derivatives thereof); local anaesthetics, such as lidocaine, prilocaine, ropivacaine, mepivacaine, bupivacaine, levobupivacaine, benzocaine, and tetracaine (and pharmaceutically acceptable salts and derivatives thereof); agents for erectile dysfunction, such as alprostadil (prostaglandin E1) (and pharmaceutically acceptable salts and derivatives thereof); anti-dandruff agents, such as selenium sulphides, piroctone oleamine and ketoconazole; anti-alopecia agents, such as minoxidil (and pharmaceutically acceptable salts and derivatives thereof); anti-acne agents, such as tretinoin (retinoic acid), adapalene, benzoyl peroxide, clindamycin, azelaic acid (and pharmaceutically acceptable salts and derivatives thereof); wound healing agents, such as fusidic acid (and pharmaceutically acceptable salts and derivatives thereof).

[0028] The cosmetically active agent for incorporation into the lipid carrier composition of the invention is preferably selected from the group consisting of: antiperspirant; antisudoral agent; antidandruff agent; glidant; moisturizing agent.

[0029] The protective agent for incorporation into the lipid carrier composition of the invention is preferably selected from the group consisting of: insect repellent; UV absorbing agent; antifungal agent; antibacterial agent; antiviral agent.

[0030] Examples of other agents for incorporation into the lipid carrier composition of the invention are: insect repellents, such as N,N-diethyl-m-toluamide (DEET), icaridine, and ethyl butyl acetylaminopropionate [and salts and derivatives thereof]; UV sunscreens, both physical and chemical, such as titanium dioxide, benzophenone-3, butyl methoxydibenzoylmethane, ethyl hexyl methoxycinnamate, and 4-aminobenzoic acid (PABA) [and salts and derivatives thereof]; tanning agents, such as dihydroxyacetone.

[0031] The cosmetically active agent for incorporation into the lipid carrier composition of the invention is preferably selected from the group consisting of: antiperspirant; antisudoral agent; antidandruff agent; glidant; moisturizing agent. Preferred antidandruff agents include piroctone oleamine and ketoconazole.

[0032] In addition to the pharmacologically active agent, the cosmetically active agent or the protective agent the respective composition of the invention can contain a counterirritant, in particular one selected from methyl salicylate, capsaicin, camphor and menthol.

[0033] According to the present invention is also disclosed a pharmaceutical composition for administration onto a surface of a living organism comprising a pharmacologically active agent in the lipid carrier composition of the invention.

[0034] According to the present invention is furthermore disclosed a cosmetic composition comprising a cosmetically active agent in the lipid carrier composition of the invention.

[0035] The pharmacologically or cosmetically active agent can be dissolved or dispersed in the carrier composition or in the silicone oil, the lower alcohol, if present, and/or the oily polar lipid used for formulating the pharmaceutical or cosmetic composition of the invention.

[0036] According to a preferred aspect of the invention the carrier composition of the invention comprises or consists of from 10 % by weight to 30 % by weight of phospholipid, from 10 % by weight to 30 % by weight of C₂ to C₄ alcohol, in particular ethanol, the remainder being a volatile silicone oil, wherein the silicone oil has a boiling point above 180°C, in particular above 200°C, and wherein the silicone oil has a heat of vaporization (kJ/kg) at 25 °C of from about 100 kJ/kg to about 300 kJ/kg, with the proviso that the content of volatile silicone oil is 50 % by weight or more.

[0037] According to a further aspect, the invention provides a lipid layer forming pharmaceutical or cosmetic composition comprising a carrier composition as described herein and a pharmacologically or cosmetically active agent or protective agent.

[0038] By addition of a desired amount of pharmaceutical, cosmetic or protective agent of the invention, in particular of from 0.01 % by weight to 2 % by weight or to 5 % by weight and even up to 15 % by weight or up to 25 by weight in respect of polar lipid, the carrier composition of the invention can be transformed into the pharmaceutical, cosmetic or protective composition of the invention.

[0039] The pharmaceutical, cosmetic or protective composition of the invention can be applied to a dry or a humid biological surface by any suitable method, such as by spraying, dipping, brushing, dropping, rubbing in.

[0040] The invention will now be described in greater detail by reference to a number of Examples illustrated in a drawing.

SHORT DESCRIPTION OF THE FIGURES

[0041]

Fig. 1

is a ternary phase diagram of a carrier composition of the invention;

Fig. 2

is a diagram showing change in transepidermal water loss (TEWL) for three compositions of the invention and vaseline as reference;

Fig. 3

is another ternary phase diagram of lipid layer forming compositions of the invention including carrier compositions and compositions comprising active agent.

DESCRIPTION OF PREFERRED EMBODIMENTS

Materials

[0042]

Table 1. Silicone oils and lipids used in the formulation experiments

Short name	Supplier, trade name	Chemical name, CAS No.	Lot No.
DC 345	Dow Corning® 345 Fluid	Dekamethylcyclopentasiloxane, 541-02-6	5627357
DC 245	Dow Corning® 245 Fluid	Dekamethylcyclopentasiloxane, 541-02-6	5480964
DC 246	Dow Corning® 246 Fluid	Dodekamethylcyclohexasiloxane, 540-97-6	5264620
DMPC	Lipoid DMPC	Dimyristoyl phosphatidylcholine, 13699-48-4	562212-1/13
DPPC	Lipoid DPPC	Dipalmitoyl phosphatidylcholine, 2644-64-6	563086-1/94
DOPC	Lipoid DOPC	Dioleoyl phosphatidylcholine, 10015-85-7	566073-1/32
DMPG	Lipoid DMPG, Na salt	Dimyristoyl phosphatidylglycerol sodium salt, 200880-40-6	602081-1/10
DPPG	Lipoid DPPG, Na salt	Dipalmitoyl phosphatidylglycerol sodium salt, 200880-41-7	603032-1/36
DMPE	Lipoid DMPE	Dimyristoyl phosphatidylethanolamine, 20255-95-2	699201-1/05
DPPE	Lipoid DPPE	Dipalmitoyl phosphatidylethanolamine, 3026-45-7	653004-1/19
DOPE	Lipoid DOPE	Dioleoylphosphatidyl ethanolamine, 2462-63-7	656006-01/012
MOG	Fluka (Sigma-Aldrich), Monoolein	Monooleoylglycerol, 25496-72-4	1384627

Short name	Supplier, trade name	Chemical name, CAS No.	Lot No.
MCM	Aarhus Karlshamn, Akoline MCM	Medium chain monoglycerides	8192270
CPL-GL	LTP, CPL [®] -Galactolipid	Chromatographically purified galactolipids	KGL06002
065	Swedish Oat Fiber, Oatwell 65 oat oil	Galactolipid enriched oat oil	PL 090219
Chol	Sigma-Aldrich, Cholesterol	Cholesterol, 57-88-5	057K0683
IPM	Croda, Crodamol IPM	Isopropyl myristate, 110-27-0	LB03845
S45	Lipoid S45	Soy bean lecithin, 8002-43-5	745303-1/926
S75	Lipoid S75	Soy bean lecithin, 8002-43-5	776132-07/918
S100	Lipoid S100	Soy bean lecithin, 8002-43-5	790551-7/910

Table 2. Active substances used in the formulation experiments*)

Active substance	CAS No.	Supplier	Lot No.
Lidocaine	137-58-6	Sigma-Aldrich	047K0080
Hydrocortisone	50-23-7	Sigma-Aldrich	010M1568
Dihydroxyacetone	96-26-4	Sigma-Aldrich	04306BJ-409
LL-37	-	PolyPeptide Laboratories A/S	1013/11
DPK-060	-	Dermagen	0508074339
Oxytocin acetate	50-56-6	Sigma-Aldrich	068K8762

*) Further information is given in the EXAMPLES

[0043] Alcohols used in the formulation experiments were ethanol 99.9 % ("EtOH", VWR), 2-propanol HPLC grade ("IPA", Rathburn), glycerol 99.5% ("Gro", VWR) and 1,2-propanediol, Ph. Eur. ("PD", Fluka/Sigma-Aldrich). The materials used in the formulation experiments were provided by the following suppliers: Dow Corning Corp., Midland, MI, USA; Lipoid GmbH, Ludwigshafen, Germany; Aarhus Karlshamn Sweden AB, Karlshamn, Sweden; LTP Lipid Technologies Provider AB, Karlshamn, Sweden; Swedish Oat Fiber AB, Varobacka, Sweden; Sigma-Aldrich, St. Louis, MO, USA; Croda, Goole, East Yorkshire, UK; Rathburn Chemicals Ltd, Walkerburn, Scotland, UK; VWR International AB, Spanga, Sweden; PolyPeptide Laboratories A/S, Hillerød, Denmark; Dermagen AB, Lund, Sweden.

[0044] EXAMPLE 1. Formulation of a local anaesthetic: lidocaine and lidocaine hydrochloride

Composition A:

Ingredient	% (w/w)
Lidocaine (Sigma L7757)	3.9
Phospholipid (Lipoid S75)	19.5
Absolute ethanol	19.5

Ingredient	% (w/w)
Volatile silicone oil (DC 345)	57.1

Composition B:

Ingredient	% (w/w)
Lidocaine hydrochloride (Sigma L5647)	2.0
Phospholipid (Lipoid S75)	20.0
Absolute ethanol	20.0
Volatile silicone oil (DC 345)	58.0

[0045] The phospholipid was dissolved in absolute ethanol at a concentration of 50.0 % (w/w). Complete dissolution of the phospholipid was promoted by short ultrasonication in a bath-type sonicator at about 40 °C.

[0046] To a pre-weighed amount of lidocaine and lidocaine hydrochloride, respectively, was added the ethanolic phospholipid solution. The mixtures were gently heated and sonicated until clear solutions had been formed. The solutions were diluted with volatile silicone oil to obtain light brown to yellow solutions, which were stored in air-tight glass vials at room temperature. The appearance of compositions (compositions A and B) was unchanged for more than a month at room temperature. No signs of phase separation or precipitation and subsequent sedimentation were observed. This indicates excellent physical stability.

EXAMPLE 2. Formulation of a local anaesthetic: benzocaine

[0047] A pre-weighed amount of benzocaine was dissolved in a 50 % (w/w) ethanolic phospholipid, prepared as described in Example 1. The solution was diluted with the volatile silicone oil. The resulting clear, light brown to yellow solution was stored in an air-tight glass vial at room temperature. The appearance of the composition (composition C) was unchanged for more than a month at room temperature. No signs of phase separation or precipitation and subsequent sedimentation were observed, which indicates excellent physical stability.

Composition C:

Ingredient	% (w/w)
Benzocaine (Fluka 06952)	4.0
Phospholipid (Lipoid S75)	20.2
Absolute ethanol	20.2
Volatile silicone oil (DC 345)	55.6

EXAMPLE 3. Formulation of an insect repellent: N,N-diethyl-m-toluamide (DEET)

[0048]

Composition D:

Ingredient	% (w/w)
DEET (Aldrich D10,095-1)	13.4
Phospholipid (Lipoid S75)	16.7
Absolute ethanol	16.7
Volatile silicone oil (DC 345)	53.2

[0049] To a pre-weighed amount of DEET was added 50 % (w/w) ethanolic phospholipid prepared as described in Example 1. The obtained clear solution was diluted with the volatile silicone oil. The resulting clear, light brown to yellow solution was stored in an air-tight glass vial at room temperature. The appearance of the composition (composition D) was unchanged for more than a month at room temperature. No signs of phase separation or precipitation and subsequent sedimentation were observed, which indicates excellent physical stability.

EXAMPLE 4. Formulation of an antifungal agent: econazole nitrate. Composition E is not within the scope of the claims.

[0050]

	Composition E:	Composition F:	Composition G
Ingredient	% (w/w)	% (w/w)	% (w/w)
Econazole nitrate (Sigma E4632)	2.3	1.1	1.5
Phospholipid (Lipoid S75)	29.1	14.5	21.2
Absolute ethanol	29.1	14.5	21.2
Volatile silicone oil (DC 345)	39.5	69.9	56.1

[0051] Three compositions (E, F, G) were prepared. To pre-weighed amounts of econazole nitrate was added 50 % (w/w) ethanolic phospholipid prepared as described in Example 1. After treatment in a bath-type sonicator at about 37 °C, the obtained clear golden brown solutions were diluted with the volatile silicone oil. The resulting clear, light golden brown solutions were stored in air-tight glass vials at room temperature. composition F was prepared by diluting a portion of composition E with volatile silicone oil.

[0052] The appearance of compositions E and F changed within a few days (slight sedimentation was observed in both samples) and therefore cannot be considered stable. On the other hand, the appearance of Composition G was unchanged for more than a month at room temperature. No signs of phase separation or precipitation and subsequent sedimentation were observed, indicating excellent physical stability.

EXAMPLE 5. Formulation of a glucocorticoid: betamethasone 17-valerate

[0053] Three compositions (H, I, J) were prepared. To pre-weighed amounts of betamethasone 17-

valerate was added 50 % (w/w) ethanolic phospholipid prepared as described in Example 1. After treatment in a bath-type sonicator at about 37 °C, clear golden brown solutions were obtained. The solutions were diluted with the volatile silicone oil and the resulting mixtures stored in air-tight glass vials at room temperature.

[0054] Composition I was prepared by diluting a portion of Composition H with volatile silicone oil. Composition I was unstable since it formed immediately a milky dispersion, which separated within a few days. Compositions H and J formed clear, light golden brown solutions. They showed no signs of phase separation or precipitation and subsequent sedimentation after storage for one month at room temperature. This indicates excellent physical stability. Composition I is not within the scope of the claims.

	Composition H:	Composition I:	Composition J
Ingredient	% (w/w)	% (w/w)	% (w/w)
Betamethasone 17-valerate (Sigma B0515)	0.5	0.1	0.1
Phospholipid (Lipoid S75)	13.3	2.7	21.1
Absolute ethanol	13.3	2.7	21.1
Volatile silicone oil (DC 345)	72.9	94.5	57.7

EXAMPLE 6. Formulation of an anti-psoriatic agent: cyclosporin A

[0055]

Composition K:

Ingredient	% (w/w)
Cyclosporin A (Sigma, 30024)	0.4
Phospholipid (Lipoid S75)	16.0
Absolute ethanol	16.0
Volatile silicone oil (DC 345)	67.6

[0056] To a pre-weighed amount of cyclosporin A was added a 50 % (w/w) ethanolic phospholipid solution, prepared as described in Example 1. After treatment in a bath-type sonicator at about 35°C, a clear solution was obtained. The solution was diluted with the volatile silicone oil to form a clear, light brown to yellow solution, which was stored in an air-tight glass vial at room temperature. The appearance of the composition (composition K) was unchanged for more than a month at room temperature. No signs of phase separation or precipitation and subsequent sedimentation were observed. This indicates excellent physical stability.

EXAMPLE 7. Formulation of an anti-alopecia agent: minoxidil

[0057] Three compositions (M, N, O) were prepared. To pre-weighed amounts of minoxidil was added

a 33 % (w/w) ethanolic phospholipid solution, ethanol, and 50 % (w/w) ethanolic phospholipid. After treatment in a bath-type sonicator at about 35 °C, the resulting mixtures were diluted with the volatile silicone oil and stored in air-tight glass vials at room temperature. Compositions N and O are not in the scope of the claims.

	Composition M:	Composition N:	Composition O:
<u>Ingredient</u>	<u>% (w/w)</u>	<u>% (w/w)</u>	<u>% (w/w)</u>
Minoxidil (Tripharma)	0.67	0.98	0.65
Phospholipid (Lipoid S75)	21.98	-	17.75
Absolute ethanol	21.98	40.27	35.49
Volatile silicone oil (DC 345)	55.37	58.75	46.11

[0058] The appearance of composition 0 stayed unchanged for more than two months at room temperature, i.e., no signs of phase separation or precipitation and subsequent sedimentation were observed. This indicates excellent physical stability. Composition M did not show complete dissolution of minoxidil, whereas Composition N started to precipitate shortly after preparation. Thus compositions M and N did not meet the criteria of one-month stability when stored in a closed container at room temperature.

EXAMPLE 8. Miscibility test

[0059] Presented in Table 3 are miscibility data of ethanolic phospholipid solutions with either volatile silicone oil or water. The mixtures with a low content of PL/ethanol in the silicone oil had a clear appearance immediately after preparation, but separated within a month at room temperature. The composition with a concentration of PL/ethanol of 20 % was miscible with the volatile silicone oil, did not change in appearance during this time period and can thus be considered to be physically stable.

Table 3. Dilution of ethanolic phospholipid (PL; Lipoid 575) solutions with volatile silicone oil (DC 345) and water, respectively. All percentages are by weight

Composition of EtOH solution	EtOH solution	Volatile silicone oil	Water	Conc. of PL	Conc. of ethanol	Conc. of diluent	Appearance directly after dilution	Appearance after one month at RT
75.0 % PL	1.01 g	1.60 g	-	29.0 %	9.7 %	61.3 %	Opaque dispersion, clear on warming	-
75.0 % PL	1.01 g	2.22 g	-	23.5 %	7.8 %	68.7 %	Opaque dispersion, clear on warming	
50.0 % PL	5.00 g	7.50 g	-	20.0 %	20.0 %	60.0 %	Clear, low-viscous light brown solution	Unchanged
50.0 % PL	5.00 g	-	7.52 g	20.0 %	20.0 %	60.0 %	Viscous gel	Unchanged

Composition of EtOH solution	EtOH solution	Volatile silicone oil	Water	Cone. of PL	Conc. of ethanol	Conc. of diluent	Appearance directly after dilution	Appearance after one month at RT
50.0 % PL	0.50 g + 4.51 g neat EtOH	7.51 g	-	2.0 %	38.0 %	60.0 %	Clear, low-viscous light yellow, opaque solution	
50.0 % PL	0.50 g	4.51 g	-	5.0 %	5.0 %	90.0 %	Clear, low-viscous light yellow solution	Phase separation
50.0 % PL	0.50 g	-	4.52 g	5.0 %	5.0 %	90.0 %	Homogeneous viscous dispersion	Unchanged
33.3 % PL	0.50 g	4.50 g	-	3.3 %	6.7 %	90.0 %	Clear, low-viscous light yellow solution	Phase separation
33.3 % PL	0.50 g	-	4.52 g	3.3 %	6.7 %	90.0 %	Homogeneous dispersion	Unchanged

[0060] The phospholipid of Table 1 is Lipoid S75 manufactured by Lipoid GmbH, Ludwigshafen, Germany. This phospholipid material from soybean contains about 68 - 73 % of phosphatidyl choline (PC). Other suitable phospholipid materials are, for example, Lipoid S45, Phospholipon 50, and Lipoid S100, all made from soybean and manufactured by Lipoid GmbH, covering a range of PC content of about 50 % up to 100 %. Further suitable phospholipids are the synthetic dioleoyl phosphatidylcholine (DOPC), dimyristyl phosphatidylcholine (DMPC), and dipalmitoyl phosphatidylcholine (DPPC).

EXAMPLE 9. Phase diagram

[0061] Fig. 1 illustrates an exemplary phase diagram of the ternary system of the polar lipid carrier composition of the invention: polar lipid (Lipoid S75)/C₂-C₄ alcohol (ethanol)/silicone oil (DC 345). Incorporation of small amounts of a pharmacologically or cosmetically active agent of the invention or of a protective agent of the invention will only insignificantly affect the area of stability. Carrier composition CC consisting of 40 % by weight of polar lipid Lipoid S75, 30 % by weight of ethanol and 30 % by weight of silicone oil DC 345 is an example of a stable carrier composition.

EXAMPLE 10. Phospholipid based carrier compositions

[0062] Phospholipid was dissolved in mixtures of DC 345 volatile silicone oil and alcohol. The lipid was accurately weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless or slightly yellow liquid was obtained. Table 4a shows examples of compositions based on phosphatidylcholines and Table 4b compositions based on phosphatidyl ethanolamines. Compositions PC-1, 2, 4, 6 and PE-1, 2, 3, 4 are not within the scope of the claims.

Table 4a. Carrier compositions based on phosphatidyl cholines

Composition	Lipid	% w/w	DC 345, % w/w	EtOH, % w/w
PC-1	DMPC	3.8	91.4	4.8
PC-2	DMPC	7.9	82.9	9.2
PC-3	DMPC	16.5	62.6	20.9
PC-4	DMPC	33.3	33.4	33.4
PC-5	DOPC	23.0	57.8	19.3
PC-6	DOPC	22.4	38.8	38.8
PC-7	DPPC	16.5	41.7	41.7

Table 4b. Carrier compositions based on phosphatidyl ethanolamines

Composition	Lipid	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
PE-1	DOPE	4.5	90.7		4.8
PE-2	DOPE	4.6	90.6	4.9	
PE-3	DOPE	7.0	83.7	9.3	
PE-4	DOPE	10.3	80.8	9.0	
PE-5	DOPE	14.9	63.8	21.3	

EXAMPLE 11. Acylglycerol based carrier compositions (not in the scope of the claims)

[0063] Commercially available monoglyceride products are mixtures of monoacyl-, diacyl- and small amounts of triacylglycerols. The acylglycerol products were dissolved in mixtures of DC 345 volatile silicone oil and alcohol. The lipid was accurately weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless liquid was obtained. Table 5 shows examples of compositions based on acylglycerols.

Table 5. Carrier compositions based on acylglycerols

Composition	Lipid	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
MG-1	MCM	13.6	86.4		
MG-2	MCM	9.8	87.5		2.7
MG-3	MCM	21.6	74.5	3.9	
MG-4	MCM	41.2	44.1	14.7	
MG-5	MOG	4.7	92.9		2.5
MG-6	MOG	4.6	91.7	3.7	
MG-7	MOG	3.6	91.6	4.8	
MG-8	MOG	9.6	81.3	9.0	
MG-9	MOG	19.0	60.7	20.2	
MG-10	MOG	38.3	30.8	30.8	

EXAMPLE 12. Carrier compositions based on cholesterol (not in the scope of the claims)

[0064] Compositions comprising cholesterol were prepared by mixing with DC 345 volatile silicone oil and alcohol. The lipid was accurately weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless liquid was obtained. Table 6 shows examples of compositions based on cholesterol.

Table 6. Carrier compositions based on cholesterol

Composition	Cholesterol, % w/w	DC 345, % w/w	EtOH, % w/w
Chol-1	1.4	88.8	9.9
Chol-2	2.1	73.4	24.5
Chol-3	3.0	48.5	48.5

EXAMPLE 13. Carrier compositions based on galactolipid rich materials (not in the scope of the claims).

[0065] Two examples of galactolipid rich materials were used to prepare mixtures with DC 345 volatile silicone oil and alcohols. The lipid was accurately weighed and mixed with silicone oil and alcohols. The mixture was gently agitated at 40 °C until a homogenous, clear and slightly yellow to brownish yellow liquid was obtained. Table 7 shows examples of compositions based on galactolipid rich lipids.

Table 7. Carrier compositions based on galactolipid rich materials

Composition	Lipid	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
GL-1	CPL-GL	4.9	71.3	23.8	
GL-2	CPL-GL	36.0	32.0	32.0	
GL-3	065	3.3	73.4	4.7	18.7

EXAMPLE 14. Carrier compositions based on lipid combinations (not in the scope of the claims)

[0066] The ability to combine lipids with different properties in volatile silicon oil/alcohol mixtures was tested. The lipid materials were accurately weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless or slightly yellow liquid was obtained. Table 8 shows examples of compositions based on various combinations of lipids.

Table 8. Carrier compositions based on lipid combinations

Composition	Lipid 1	% w/w	Lipid 2	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
Comb-1	IPM	8.9	DOPC	8.3	78.7	4.1	
Comb-2	IPM	9.0	DOPE	5.2	81.5	4.3	
Comb-3	MCM	6.9	DOPC	5.8	82.9	4.4	
Comb-4	MOG	10.3	DOPC	0.9	85.1		3.7
Comb-5	MCM	8.9	Chol	1.0	79.8	10.3	

Composition	Lipid 1	% w/w	Lipid 2	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
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EXAMPLE 15. Carrier compositions based on commercially available lecithin

[0067]

Table 9. Carrier compositions based on lecithin. The compositions Lec-1, 2, 4-9 and 11 are not within the scope of the claims.

Composition	Lecithin	% w/w	DC 345, % w/w	EtOH, % w/w	IPA, % w/w
Lec-1	S45	5.6	89.7	4.7	
Lec-2	S45	9.9	81.1	9.0	
Lec-3	S45	30.3	52.3	17.4	
Lec-4	S45	35.8	32.1	32.1	
Lec-5	S75	14.8	76.5	4.0	4.7
Lec-6	S75	25.4	63.4	7.0	4.2
Lec-7	S75	16.3	75.3	8.4	
Lec-8	S75	43.4	42.5	14.2	
Lec-9	S75	39.3	30.4	30.4	
Lec-10	S100	13.1	65.2	21.7	
Lec-11	S100	27.3	36.3	36.3	

[0068] Commercially available lecithin products are in mixtures of polar lipids (mainly phospholipids) and non-polar lipids (mainly triglycerides). The materials used in the following examples are all obtained from soy beans and contain phosphatidyl choline as the main polar lipid. The lipid was accurately weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and yellow or brownish yellow liquid was obtained. Table 9 shows examples of compositions based on lecithins.

EXAMPLE 16. Carrier compositions with different silicone oils (not in the scope of the claims)

[0069] The possibility to use different volatile silicone oils was tested by replacing DC 345 by two other silicone oils, DC 245 and DC 246. The lipid was weighed and mixed with silicone oil and alcohol. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless liquid was obtained. Table 10 shows examples of compositions comprising DC 245 and DC 246.

Table 10. Carrier compositions with volatile silicone oils DC 245 and DC 246

Composition	Silicone oil	% w/w	Lipid	% w/w	EtOH, % w/w	IPA, %w/w
Sil-1	DC245	81.8	DOPE	9.1	9.1	
Sil-2	DC245	88.0	MCM	5.1		6.9

Composition	Silicone oil	% w/w	Lipid	% w/w	EtOH, % w/w	IPA, %w/w
Sil-3	DC245	94.0	MCM	2.2		3.8
Sil-4	DC246	83.3	DOPE	7.4	9.3	

EXAMPLE 17. Carrier compositions based on lipids and small amounts of water (not within the scope of the claims)

[0070]

Table 11. Carrier compositions with small amounts of water

Composition	Lipid	% w/w	Water, o/o w/w	DC345, o/o w/w	EtOH, % w/w	IPA, % w/w
Wat-1	DM PC	7.0	4.7	79.5	8.8	
Wat-2	DMPG	2.3	5.3	69.4	23.1	
Wat-3	DOPE	6.8	2.5	58.1	14.9	17.7
Wat-4	S75	9.7	4.4	53.7	10.8	21.5
Wat-5	S75	5.5	2.0	72.9	8.1	11.4

[0071] The possibility to add small amounts of water to the vehicles of the invention was tested. The lipid was accurately weighed and mixed with silicone oil and alcohol. A small amount of water and optionally isopropanol was added. The mixture was gently agitated at 40 °C until a homogenous, clear and colourless or brownish yellow liquid was obtained. Table 11 shows examples of compositions with small amounts of water.

EXAMPLE 18. DPK-060 peptide compositions in silicone oil/lipid vehicles (not within the scope of the claims)

[0072] Accurately weighed amounts of the peptide DPK-060 were dissolved in mixtures of lipid, glycerol, 1,2-propanediol and ethanol at 40 °C under agitation. Silicone oil (DC 345) and isopropanol was added and the mixture was gently agitated at 40 °C until a homogenous, clear and colourless to brownish yellow liquid was obtained. Table 12 presents representative examples of DPK-060 compositions.

Table 12. DPK-060 peptide compositions in silicone oil/ lipid vehicles

Composition	DPK-060 % w/w	Lipid	% w/w	Gro % w/w	PD % w/w	DC 345 % w/w	EtOH % w/w	IPA % w/w	%active/ nonvol.*
KL-DPK-21	0.033	S75	3.9	6.4		58.2	13.0	18.5	0.32
KL-DPK-22	0.199	S75	5.7	10.1	2.8	39.3	12.5	29.3	1.06
KL-DPK-23	0.056	S45	3.9	6.6		56.8	12.5	20.1	0.53
KL-DPK-24	0.129	S45	5.8	9.8	2.9	39.5	12.6	29.3	0.69
KL-DPK-25	0.095	DOPC	3.8	6.6		56.2	13.0	20.3	0.90

Composition	DPK-060 % w/w	Lipid	% w/w	Gro % w/w	PD % w/w	DC 345 % w/w	EtOH % w/w	IPA % w/w	%active/ nonvol.*
KL-DPK-26	0.272	DOPC	6.8	10.3	2.8	40.8	13.1	26.0	1.34
KL-DPK-27	0.036	065	4.0	6.3		54.3	11.6	23.7	0.35
KL-DPK-28	0.058	065	5.6	9.6	2.8	38.9	11.4	31.5	0.32
KL-DPK-29	0.096	DOPE	4.4	6.9		57.8	12.9	17.9	0.84
KL-DPK-31	0.125	DMPC	4.3	6.4		57.1	12.7	19.3	1.15
KL-DPK-40	0.167	S75	4.6	6.3	6.1	42.6	13.9	26.3	0.98
KL-DPK-42	0.184	S45	5.7	10.1	2.9	40.0	11.5	29.5	0.97
KL-DPK-43	0.188	DOPC	5.7	9.5	3.7	40.9	11.9	28.0	0.98
KL-DPK-45	0.192	DOPE	5.9	10.3	3.1	41.7	11.8	27.1	0.99
KL-DPK-47	0.189	DMPC	5.9	10.2	3.1	40.9	11.5	28.2	0.97
KL-DPK-49	0.168	SM	4.1	6.5		56.0	12.7	20.6	1.57
KL-DPK-50 (placebo)		S75	4.7	6.2	6.1	42.8	13.7	26.4	
KL-DPK-51 (placebo)		DOPE	4.2	6.6		58.9	13.2	17.1	
KL-DPK-52	0.105	DOPE	4.0	6.6		57.6	13.0	18.7	0.98
KL-DPK-53	0.107	DMPC	4.2	6.6		58.3	13.0	17.7	0.97
* Concentration of DPK-060 in % w/w of the non-volatile part of the composition									

EXAMPLE 19. LL-37 peptide compositions in silicone oil/lipid vehicles (not in the scope of the claims)

[0073] Accurately weighed amounts of the peptide LL-37 were dissolved in mixtures of lipid, glycerol and ethanol at 40 °C under agitation. Silicone oil (DC 345) and isopropanol was added and the mixture was gently agitated at 40 °C until a homogenous, clear and slightly yellow to brownish yellow liquid was obtained. Table 13 presents representative examples of LL-37 compositions.

Table 13. LL-37 peptide compositions in silicone oil/lipid vehicles

Composition	LL-37 % w/w	Lipid	% w/w	Gro % w/w	DC345 % w/w	EtOH % w/w	IPA % w/w	% active/ nonvol*
KL-LL37-1	0.202	S75	6.9	7.1	48.5	23.3	14.0	142
KL-LL37-2	0.184	DOPE	5.3	8.0	49.3	26.2	11.1	1.37
* Concentration of LL-37 in % w/w of the non-volatile part of the composition								

EXAMPLE 20. Oxytocin compositions in silicone oil/lipid vehicles (not in the scope of the claims)

[0074] Accurately weighed amounts of oxytocin were dissolved in mixtures of lipid, glycerol and ethanol at 40 °C under agitation. Silicone oil (DC 345) and optionally isopropanol was added and the mixture was gently agitated at 40 °C until a homogenous, clear and colourless to brownish yellow liquid was obtained. Table 14 presents representative examples of oxytocin compositions.

Table 14. Oxytocin compositions in silicone oil/lipid vehicles

Composition	Oxytocin % w/w	Lipid 1	% w/w	Lipid 2	% w/w	Gro % w/w	DC345 % w/w	EtOH % w/w	IPA % w/w	% active/ nonvol*
Ox-1	0.139	DOPE	5.9	MCM	10.8		70.6	12.6		0.83
Ox-2	0.090	DOPE	4.4	MCM	10.0	8.1	46.4	8.3	22.8	0.40
Ox-3	0.126	MCM	22.1				66.3	11.5		0.56
Ox-4	0.094	MCM	3.9			8.6	48.8	7.1	31.5	0.74
Ox-5	0.078	MCM	5.1				58.2	23.4	13.2	1.51
Ox-6	0.100	MOG	25.6				64.0	10.3		0.39
Ox-7	0.161	S75	6.6				80.0	13.3		2.40
Ox-8	0.088	S75	5.0			8.5	51.7	8.6	26.1	0.65
Ox-9	0.129					8.6	51.0	8.9	31.4	1.47
Ox-10	0.178						85.8	14.4		100
* Concentration of oxytocin in % w/w of the non-volatile part of the composition										

EXAMPLE 21. Hydrocortisone compositions in silicone oil/lipid vehicles (not in the scope of the claims)

[0075] An accurately weighed amount of hydrocortisone was dissolved in a mixture of lipid and ethanol at 40 °C under agitation. Silicone oil (DC 345) and isopropanol was added and the mixture was gently agitated at 40 °C until a homogenous, clear and yellow liquid was obtained. Table 15 presents a representative example of hydrocortisone compositions.

Table 15. Hydrocortisone composition in silicone oil/lipid vehicles

Composition	drocortisone % w/w	Lipid	% w/w	DC 345 % w/w	EtOH % w/w	IPA % w/w	% active/ nonvol*
HC-1	0.093	S75	4.8	65.2	14.8	15.1	1.93
*Concentration of hydrocortisone in % w/w of the non-volatile part of the composition							

EXAMPLE 22. Dihydroxyacetone compositions in silicone oil/ lipid vehicles (not in the scope of the claims)

[0076] An accurately weighed amount of dihydroxyacetone was dissolved in a mixture of lipid and ethanol at 40 °C under agitation. Silicone oil (DC 345) and isopropanol was added and the mixture was

gently agitated at 40 °C until a homogenous, clear and yellow liquid was obtained. Table 16 presents a representative example of dihydroxyacetone compositions.

Table 16. Dihydroxyacetone composition in silicone oil/lipid vehicles

Composition	Dihydroxyacetone % w/w	Lipid	% w/w	DC 345 % w/w	EtOH % w/w	IPA % w/w	% active/ nonvol*
DA-1	103	MCM	4.4	76.8	8.9	8.8	19.0
* Concentration of dihydroxyacetone in % w/w of the non-volatile part of the composition.							

EXAMPLE 23. Lidocaine compositions in silicone oil/lipid vehicles (Compositions KL-LK-1, 2, 7, 9-11, 13, 14 and 16 are not in the scope of the claims)

[0077] An accurately weighed amount of lidocaine was dissolved in a mixture of lipid and ethanol at 40°C under agitation. Silicone oil (DC 345) and optionally isopropanol was added and the mixture was gently agitated at 40 °C until a homogenous, clear and colourless to yellow liquid was obtained. Table 17 presents representative examples of lidocaine compositions.

Table 17. Lidocaine compositions in silicone oil/lipid vehicles

Composition	Lidocaine %/w/w	Lipid 1	% w/w	Lipid 2	% w/w	DC 345 % w/w	EtOH % w/w	IPA % w/w	% active/ nonvol*
KL-LK-1	0.7	S75	7.6			65.4	7.5	18.8	8.8
KL-LK-2	0.8	S75	2.8			59.8	11.4	25.3	22.2
KL-LK-6	11.5	S75	13.7			65.3	9.5		45.8
KL-LK-7	5.1	DOPE	1.3			88.7	5.0		79.9
KL-LK-8	5.1	DOPE	10.2			74.9	9.8		33.0
KL-LK-9	4.7	MCM	1.1	Chol	0.5	87.8	5.9		74.4
KL-LK-10	4.8					90.3	4.9		100
KL-LK-11	5.0	MCM	8.9	Chol	1.0	75.2	10.0		33.5
KL-LK-12	5.0	S75	15.0			70.1	9.9		25.0
KL-LK-13	5.0	DOPE	5.2			79.6	10.2		48.7
KL-LK-14	5.0					85.0	10.0		100
KL-LK-16	20.2	MCM	20.8			50.4	8.6		49.4
* Concentration of lidocaine in % w/w of the non-volatile part of the composition									

EXAMPLE 24. Control of transepidermal water loss

[0078] Three lipid layer forming compositions of the invention termed A, B, C (Table 18) were tested for their effect on transepidermal water loss (TEWL) from a skin surface. Their effect was compared with that of white vaseline (ACO hud, Sweden), a conventional agent for TEWL. The compositions were applied to the skin of ten healthy individuals, 5 women and 5 men; mean age 34 years, SD 18 years,

who showed no evidence of skin disease. Prior to application, the volar aspects of their forearms were rapidly cleansed with paper tissue soaked in pure alcohol. Five rectangular areas of 2 x 2 cm were marked on the volar forearm with a pencil and measured for basal TEWL. The compositions and vaseline were applied to the areas in a randomized manner; one of the areas was left as an untreated control. Two dosages were studied, 3 $\mu\text{l}/\text{cm}^2$ and 6 $\mu\text{l}/\text{cm}^2$. Vaseline was used in half of the amount, i.e. 1.5 $\mu\text{l}/\text{cm}^2$ and 3 $\mu\text{l}/\text{cm}^2$. The high dose was applied on the right forearm, and the low dose on the left forearm. The products were dispensed onto the surface by means of a displacement micro-pipette (Gilson). The compositions were applied in small droplets onto the area; evaporation was facilitated by slightly blowing at the surface. Vaseline was spread by fingertip.

Table 18. Compositions tested for control of transepidermal water loss (% by weight) (Compositions 2 and 3 are not within the scope of the claims)

Composition #	MCM	Polar lipid	EtOH	DC345
1		15 (S75)	10	75
2	9	1 (Chol)	10	80
3		5 (DOPE)	10	85

[0079] TEWL was measured before application and 30 min after application by use of DermaLab equipment (open chamber; Cortex Technology, Hadsund, Denmark). The recorded reduction of transepidermal water loss is shown in Fig. 2. The composition 1 of the invention was comparable in effect to Vaseline while compositions 2 and 3 exerted no significant effect on TEWL.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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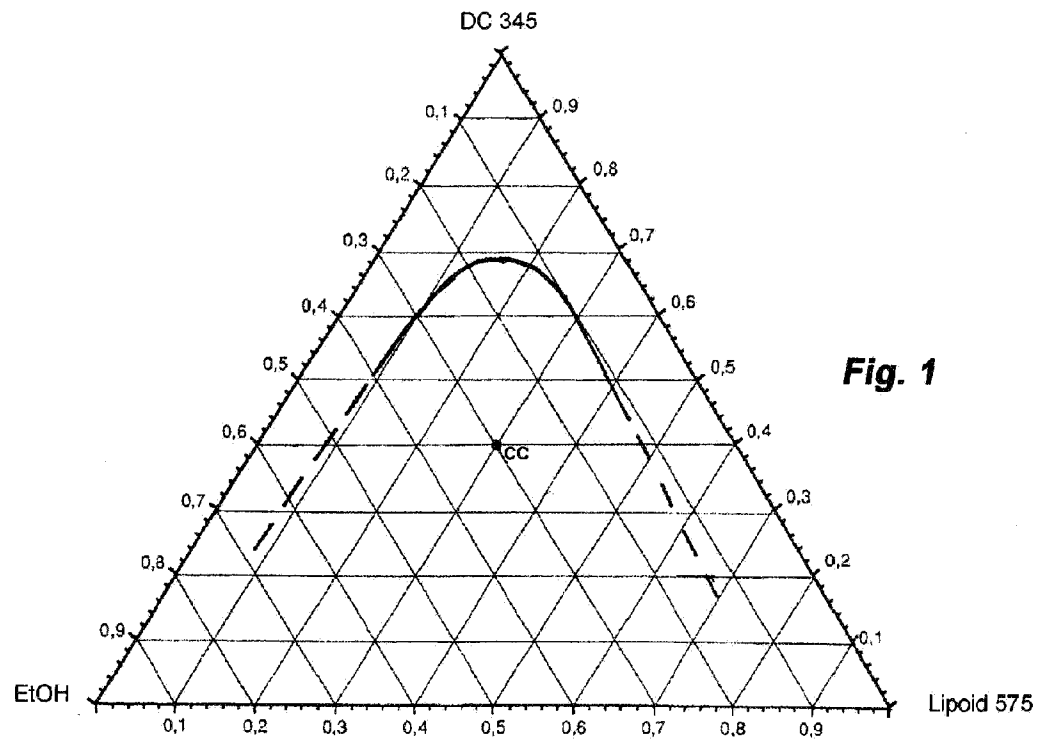
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- [WO9944585A1](#) **[0022]**

P A T E N T K R A V

1. Bærersammensætning til topikal administration som danner et lipidlag på hud eller slimhinde, omfattende flygtig silikoneolie, fra 10 vægtprocent til 30 vægtprocent af phospholipid, fra 10 vægtprocent til 30 vægtprocent af ethanol, eventuelt vand i en mængde på 5 vægtprocent eller mindre, hvor silikoneolien har et kogepunkt over 180 °C, især over 200 °C, og hvor silikoneolien har en fordampningsvarme (kJ/kg) ved 25 °C på fra omkring 100 kJ/kg til omkring 300 kJ/kg, med betingelsen at indholdet af flygtig silikoneolie er 50 vægtprocent eller mere.
2. Sammensætning ifølge krav 1, hvor silikoneolien har en fordampningsvarme (kJ/kg) ved 25 °C på fra 120 kJ/kg til 200 kJ/kg, især på fra 140 kJ/kg til 180 kJ/kg.
3. Sammensætning ifølge krav 1 eller 2, hvor den flygtige silikoneolie omfatter én af dekamethylcyclopentasiloxan og dodekamethylcyclohexasiloxan.
4. Sammensætning ifølge krav 1 eller 2, hvor den volatile silikoneolie omfatter én af heptasiloxan og octasiloxan.
5. Sammensætning ifølge et hvilket om helst af krav 1 til 4, omfattende mindre end 1 vægtprocent vand.
6. Lipidlagsdannende farmaceutisk eller kosmetisk sammensætning omfattende en bærersammensætning ifølge et hvilket som helst af krav 1 til 5 og et farmakologisk eller kosmetisk aktivt middel eller beskyttende middel.
7. Sammensætning ifølge krav 6, hvor midlet er et farmakologisk aktivt middel valgt fra gruppen bestående af: antimikrobielt middel, antibiotika; antimykotisk middel; antibakterielt middel; antisvampemiddel; antiviralt middel; antiseptika; antibetændelsesmiddel; kløestillende middel; antipsoriasismiddel; hostestillende middel; antiallopeciamiddel; antiaknemiddel; antiinflammatorisk middel; antimavesårsmiddel; lokalbedøvelsesmiddel.
8. Sammensætning ifølge krav 6, hvor midlet er et kosmetisk aktivt middel valgt fra gruppen bestående af: antiperspirant; antisvedmiddel; antiskælmiddel; glidemiddel; fugtgivende middel.
9. Sammensætning ifølge krav 6, hvor midlet er et beskyttelsesmiddel valgt fra gruppen bestående af: UV-absorberende middel, insektafskrækkelsesmiddel, antibakterielt middel, antisvampemiddel; antiviralt middel, antinematodemiddel.
10. Sammensætning ifølge et hvilket som helst af krav 1 til 9, til at styre transepidermalt vandtab.

DRAWINGS



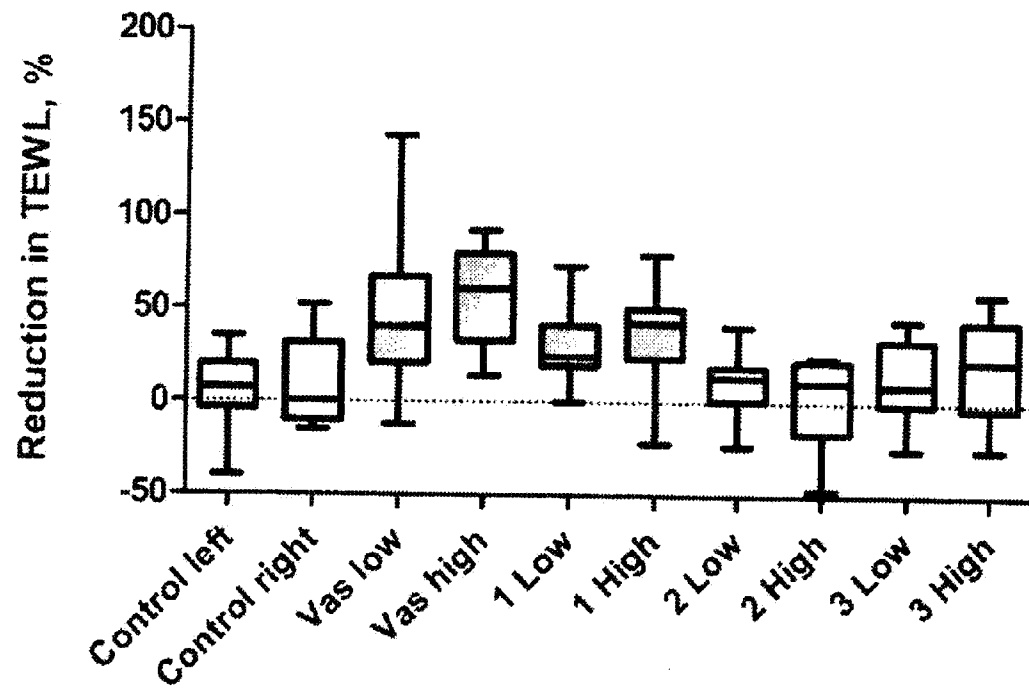


Fig. 2

