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(54) Titre : COMPOSITION TOPIQUE ET VEHICULE POUR L'ADMINISTRATION DE PRINCIPES ACTIFS PHARMACEUTIQUES OU COSMETIQUES

(54) Title: TOPICAL COMPOSITION AND CARRIER FOR ADMINISTRATION OF PHARMACEUTICALLY OR COSMETICALLY ACTIVE INGREDIENTS

(57) Abrégé/Abstract:
The present invention provides topical pharmaceutical or cosmetic compositions comprising a pharmaceutical or cosmetic carrier comprising at least 3% by weight of phospholipid; at least 20 % by weight of C_2-C_4 alcohol;at least 0.05 % by weight keratolytic agent; and optionally,comprising up to 2 % by weight of water;and pharmacologically or cosmetically active agent dissolved in said carrier. The compositions are sprayable. Also disclosed is a method of preparing the composition and use thereof, as well as the pharmaceutical or cosmetic carriers as such.

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(54) Title: TOPICAL COMPOSITION AND CARRIER FOR ADMINISTRATION OF PHARMACEUTICALLY OR COSMETICALLY ACTIVE INGREDIENTS

(57) Abstract: The present invention provides topical pharmaceutical or cosmetic compositions comprising a pharmaceutical or cosmetic carrier comprising at least 3% by weight of phospholipid; at least 20 % by weight of C_2-C_4 alcohol;at least 0.05 % by weight keratolytic agent; and optionally,comprising up to 2 % by weight of water;and pharmacologically or cosmetically active agent dissolved in said carrier. The compositions are sprayable. Also disclosed is a method of preparing the composition and use thereof, as well as the pharmaceutical or cosmetic carriers as such.

TOPICAL COMPOSITION AND CARRIER FOR ADMINISTRATION OF PHARMACEUTICALLY OR COSMETICALLY ACTIVE INGREDIENTS

Field of the invention

The present invention relates to topical pharmaceutical or cosmetic compositions comprising a pharmaceutical or cosmetic carrier, to methods for their manufacture and to the use of said composition.

Background of the invention

In the pharmaceutical and cosmetic field of topical formulations there is a need of a carrier capable of incorporating a pharmacologically or cosmetically active agent. Furthermore there is a need of a corresponding topical composition for administration comprising pharmacologically or cosmetically active agent. It is desirable that the composition can be applied onto the skin so as to form a thin coherent layer. To facilitate application, such as by spraying, the composition should be of low viscosity. The composition should furthermore facilitate the deposition of pharmacologically or cosmetically active agents to the skin. The composition should also have an acceptable shelf life.

WO 2010/036947 A2 discloses a lipid based pharmaceutical composition for topical administration comprising one or more lipids and one or more pharmaceutically active compounds selected from the group consisting of finasteride, duasteride, minoxidil, amphotericin B and tacrolimus.

EP 1 787 658 A1 discloses a sustained release formulation for subcutaneous or intramuscular administration, comprising somatostatin analogue inhibitor of growth hormone, C_1-C_8 alcohol, phospholipid, and C_1-C_4 alkyl fatty acid ester.

JP 2008-163010 discloses a non-aqueous stock solution containing phosphatide (phospholipid) and C_2-C_5 aliphatic alcohol, combined with a

propellant which contains 50 weight % or more of dimethyl ether. The stock solution can contain 0.005 to 4 weight % of phosphatide.

US 2002/0076423 relates to cooling cosmetic or dermatological formulations which reduce the secondary reactions of the skin to the effect of UV radiation, containing chitosan and lecithin. Compositions exemplified are emulsions containing at least 25 % of water.

Disclosure of the invention

It is an object of the invention to provide a carrier and a composition, which is easily applicable onto the skin, such as by spraying.

Still an object of the invention is to provide a carrier capable of incorporating a pharmacologically and cosmetically active agent.

Still an object of the invention is to provide a composition capable of forming a stable coherent layer on the skin of an animal, such as a mammal, including humans.

Still an object of the invention is to provide a composition in which the components are physically and chemically stable during an acceptable shelf life. Further objects of the invention will be evident from examples.

The present invention is directed to a pharmaceutical or cosmetic carrier comprising or consisting of a phospholipid, a C_2-C_4 alcohol, and a keratolytic agent. In one aspect of the invention the carrier may comprise a small amount of water, such as one or two percent of weight.

An aspect of the present invention is a topical pharmaceutical or cosmetic composition comprising a carrier as disclosed herein, and a pharmacologically or cosmetically active agent dissolved therein. The topical pharmaceutical or cosmetic composition of the invention can be formed by

dissolving a pharmacologically or cosmetically active agent in the carrier as disclosed and claimed herein.

The present invention is based on the insight that lower alcohol, in particular a C_2-C_4 alcohol, can be advantageously used as the evaporating component, in particular the single evaporating component, of a composition for topical administration comprising a phospholipid, a keratolytic agent and a pharmacologically or cosmetically active agent. Preferred lower alcohol includes ethanol, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol.

Phospholipids of the invention include, but not limited to, commercial pharmaceutical or cosmetic grade phospholipid, and can be natural or synthetic. A person skilled in the art is aware of that phospholipid from commercial sources comprises substantial amounts of other lipids. Phospholipid useful in accordance with the invention may contain substantial amounts of non-polar lipids. It may be composed of up to about 50 % by weight of mono-, di- and triglycerides. Natural phospholipids include, but are not limited to, lecithins from soybeans, rape seeds, sunflower seeds and eggs. A preferred phospholipid of the invention is phosphatidylcholine (PC), a major constituent of cell membranes.

Keratolytic agents of the invention include α- and β-hydroxy acids, such as glycolic acid, lactic acid, malic acid, and salicylic acid and pharmaceutically acceptable salts thereof. Preferred keratolytic agents of the invention are allantoin, urea and sulphur. A particularly preferred keratolytic agent is urea.

The carriers and compositions of the invention are clear colorless, light yellow or brownish yellow fluids that can be stored for long periods of time, even at elevated temperatures, such as 30 °C or 40 °C, without change in physical appearance, such as precipitation, cloudiness or phase separation.

The clear appearance and low viscosity of the carrier and composition of the invention seems to be due to the inability of phospholipids to form lyotropic liquid crystals, such as lamellar and hexagonal of high viscosity in the solvent system used. The carrier and the pharmaceutical or cosmetic composition of the invention are clear and of low viscosity even at concentrations of phospholipid as high as 50-60 % by weight. In contrast, phospholipid compositions corresponding to those of the invention, but which contain substantial amounts of water, are slightly viscous dispersions at low polar lipid concentrations or thick gels at higher polar lipid concentrations. The high viscosity of the latter composition does not allow administration by spraying.

The low viscosity of the carrier and composition of the invention makes them suitable for spraying by a pump device instead of using propellants and pressurized containers.

The pharmacologically active agent of the invention is 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; antiphlogistics; analgesic; antiulcer agent; local anaesthetic; immune response modifying agent.

More particularly, the pharmacologically active agent of the invention is selected from: antibacterial agents, such as oxytetracycline, fusidic acid, gentamycine, 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 phosphoneformate hexahydrate) and docosanol (and pharmaceutically acceptable salts and derivatives thereof); antiseptics, such

as chlorhexidine, benzalkonium chloride and hydrogen peroxide; anti-inflammatory agents (glucocorticoids), such as hydrocortisone, clobetasone, triamcinolone, betamethasone, mometasone, desonide, prednisolone and clobetasol (and pharmaceutically acceptable salts and derivatives thereof); antiphlogistics/analgesics (NSAID's), such as acetylsalicylic acid, diclofenac, ketoprofen, ibuprofen, naproxen, capsaicin and nicotinate (and pharmaceutically acceptable salts and derivatives thereof); antipruritic agents, such as glucocorticoids, for example, hydrocortisone, clobetasone, clobetasol, desonide, mometasone and betamethasone, and local anaesthetics, for example, lidocaine, prilocaine, ropivacaine, mepivacaine, bupivacaine, levobupivacaine, benzocaine, and tetracaine (and pharmaceutically acceptable salts and derivatives thereof); antipsoriatic agents, such as calcipotriol, calcitriol, 7-dehydrocholesterol, cholecalciferol, maxacalcitol, doxercalciferol, paricalcitol, inecalcitol, eldecalcitol, tacalcitol, betamethasone 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); antiglaucomateous agents, such as timolol, betaxolol, latanoprost, bimatoprost, and travoprost (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 retinol, tretinoin (retinoic acid), isotretinoin, adapalene, motretinide, benzoyl peroxide, clindamycin azelaic acid and lauric acid (and pharmaceutically acceptable salts and derivatives thereof); wound healing agents, such as pantothenic acid and fusidic acid (and pharmaceutically acceptable salts and derivatives thereof); steroid hormones, such as prednisone, dexamethasone, estradiol, triamcinolone, fludrocortisone, testosterone, distilbestrol; peptide homones, such as oxytocin, LL-37, DPK-

060 and PXL-01 (and pharmaceutically acceptable salts and derivatives thereof).

The cosmetically active agent of the invention is preferably selected from the group consisting of: antiperspirant; antisudoral agent; antidandruff agent; glidant and moisturizing agent.

According to one aspect of the invention the pharmaceutical or cosmetic carrier comprises or substantially consists of 30 % by weight to 75 % by weight of a phospholipid, from 20 % by weight to 60 % by weight of a C_2 to C_4 alcohol, from 0.05 % by weight to 10 % by weight of a keratolytic agent, and optionally 1-2 % by weight of water, adding up to 100 %.

According to another aspect of the invention the pharmaceutical or cosmetic carrier comprises or substantially consists of 30 % by weight to 65 % by weight of a phospholipid, from 30 % by weight to 60 % by weight of a C_2 to C_4 alcohol, from 0.05 % by weight to 10 % by weight of a keratolytic agent and optionally 1-2 % by weight of water, adding up to 100 %.

According to another aspect of the invention the weight ratio of phospholipid to C_2 to C_4 alcohol of the carrier is from 1.5:1 to 1:1.5 or from 1.2:1 to 1:1.2, such as about 1:1, the carrier consisting of 90 % by weight or more of phospholipid and C_2 to C_4 alcohol in combination, of 10 % by weight or less of a keratolytic agent and, optionally, of up to 1 % by weight or up to 2 % by weight of water, the combined contents adding up to 100 %.

According to another aspect of the invention the pharmaceutical or cosmetic composition of the invention comprises or substantially consists of 30 % by weight to 75 % by weight of phospholipid, from 20 % by weight to 60 % by weight of C_2 to C_4 alcohol, from 0.05 % by weight to 10 % by weight of a keratolytic agent, from 0.001 % by weight to 5 % by weight, exceptionally up

to 8 % by weight, of pharmacologically or cosmetically active agent, and optionally 1-2 % by weight of water, adding up to 100 %.

According to another aspect of the invention the pharmaceutical or cosmetic composition comprises or substantially consists of 40 % by weight to 65 % by weight of a phospholipid, from 30 % by weight to 60 % by weight of a C_2 to C_4 alcohol, from 0.05 % by weight to 10 % by weight of a keratolytic agent, from 0.001 % by weight to 5 % by weight, exceptionally up to 8 % by weight, of a pharmacologically or cosmetically active agent and optionally 1-2 % by weight of water, adding up to 100 %.

According to another aspect of the invention the weight ratio of phospholipid to C_2 to C_4 alcohol of the pharmaceutical or cosmetic composition is from 1:1.5 to 1.5:1 or from 1:1.2 to 1.2:1, such as about 1:1, the composition consisting of 85 % by weight or more of phospholipid and C_2 to C_4 alcohol in combination, of 10 % by weight or less of keratolytic agent, of up to 5 % by weight and, exceptionally, up to 8 % by weight of pharmacologically or cosmetically active agent and, optionally, of up to 1 % by weight or up to 2 % by weight of water, the combined components adding up to 100 %.

According to an aspect of the invention, there is provided a topical pharmaceutical or cosmetic composition comprising a pharmaceutical or cosmetic carrier comprising
at least 3 % by weight of a phospholipid;
at least 20 % by weight of a C_2-C_4 alcohol;
at least 0.05 % by weight of a keratolytic agent; and
optionally, comprising up to 2 % by weight of water; and pharmacologically or cosmetically active agent dissolved in said carrier.

In one embodiment of the invention, said composition comprises from 3 % by weight to 60 % by weight of a phospholipid; from 20 % by weight to 90 % by weight of a C_2-C_4 alcohol; from 0.05 % by weight to 15 % by weight of a

keratolytic agent; from 0.001 % by weight to 8 % by weight of pharmacologically or cosmetically active agent; optionally further comprising water up to 2 % by weight; wherein the components are added up to a total of 100% by weight.

In another embodiment of the invention, said composition comprises from 5 % by weight to 55 % by weight of a phospholipid, from 30 % by weight to 85 % by weight of a C_2-C_4 alcohol; from 0.05 % by weight to 10 % by weight of a keratolytic agent; from 0.001 % by weight to 8 % by weight of a pharmacologically or cosmetically active agent; optionally further comprising water up to 2 % by weight; wherein the components are added up to a total of 100% by weight.

In another embodiment of the invention, said composition comprises 5-20 % by weight of a phospholipid.

In another embodiment of tthe invention, said composition comprises 10-20 % by weight of a phospholipid.

In another embodiment of the invention, said composition comprises about 5, 6, 7, 8, 9 or 10 % by weight of a phospholipid.

In another embodiment ofthe invention, said composition comprises 70-90 % by weight of a C_2-C_4 alcohol.

In another embodiment of the invention, said composition comprises 0.5-8 % by weight of a keratolytic agent.

In another embodiment of the invention, said C_2-C_4 alcohol is ethanol.

In another embodiment of the invention, said phospholipid comprises or substantially consists of phosphatidylcholine (PC).

In another embodiment of the invention, said keratolytic agent is selected from the group consisting of glycolic acid; lactic acid; malic acid; salicylic acid; allantoin; urea and sulphur.

In another embodiment of the invention, said keratolytic agent is urea.

In another embodiment of the invention, said pharmacologically active agent is selected from 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; antiphlogistics; analgesic; antiulcer agent; local anaesthetic and immune response modifying agent.

In another embodiment of the invention, said pharmacologically active agent is a peptide.

In another embodiment of this aspect, said cosmetically active agent is selected from an antiperspirant; an antisudoral agent; an antidandruff agent; a glidant and a moisturizing agent.

In another embodiment of the invention, said composition is in sprayable form.

According to an aspect of the invention, there is provided a topical pharmaceutical or cosmetic carrier comprising a phospholipid, a C_2-C_4 alcohol, and a keratolytic agent, the carrier comprising of
at least 5 % by weight of a phospholipid;
at least 20 % by weight of a C_2-C_4 alcohol;
at least 0.05 % by weight of a keratolytic agent; and
optionally, comprising up to 2 % by weight of water.

In one embodiment of the invention, said carrier comprises from 5 % by weight to 60 % by weight of a phospholipid; from 20 % by weight to 90 % by weight of a C_2-C_4 alcohol; and from 0.05 % by weight to 15 % by weight of a keratolytic agent.

In another embodiment of the invention, said carrier comprises from 10 % by weight to 55 % by weight of a phospholipid, from 30 % by weight to 85 % by weight of a C_2-C_4 alcohol; and from 0.05 % by weight to 10 % by weight of a keratolytic agent.

In another embodiment of the invention, said carrier comprises from about 5, 6, 7, 8, 9 or 10 % by weight of a phospholipid.

In another embodiment of the invention, said carrier comprises 5-20 % by weight of a phospholipid.

In another embodiment of the invention, said carrier comprises 10-20 % by weight of a phospholipid.

In another embodiment of the invention, said carrier comprises 70-90 % by weight of a C_2-C_4 alcohol.

In another embodiment of the invention, said carrier comprises 0.5-8 % by weight of a keratolytic agent.

In another embodiment of the invention, said C_2-C_4 alcohol is ethanol.

In another embodiment of the invention, said phospholipid comprises or substantially consists of phosphatidylcholine (PC).

In another embodiment of the invention, said keratolytic agent is selected from the group consisting of glycolic acid; lactic acid; malic acid; salicylic acid; allantoin; urea and sulphur.

In another embodiment of the invention, said keratolytic agent is urea.

In another embodiment of the invention, said carrier is stable for at least 3 months of storage, at room temperature.

According to an aspect of the invention, there is provided a method of preparing a topical pharmaceutical or cosmetic composition according to the present invention, comprising:
(a) providing carrier according to the present invention;
(b) admixing a pharmaceutically or cosmetically active agent;
(c) agitating said mixture obtained in step (b), optionally under heating, until a clear liquid has been formed.

According to an aspect of the invention, there is provided the use of a topical pharmaceutical composition according to the present invention, for administration of a pharmacologically active agent contained therein. Said administration may be by spraying.

According to an aspect of the invention, there is provided the use of a topical cosmetic composition according to the present invention, for administration of an active agent contained therein. Said administration may be by spraying.

According to an aspect of the invention, there is provided veterinary use of a topical pharmaceutical or cosmetic composition according to the present invention, for administration of an active agent contained therein. Said administration may be by spraying.

According to an aspect of the invention, there is provided a method of treating a disease in a patient or animal in need thereof comprising topically administering a pharmaceutical composition according to the present invention, said composition comprising a therapeutically active amount of a pharmacologically active ingredient. Said administration may be topically administered by spraying.

The carrier of the invention is particularly suited for incorporation of pharmacologically active peptides such as protease inhibitors, insulin, growth hormone, interferons, interleukins, pentagetide, histamine releasing peptide antigen, antiflammins, corticotropin releasing factor, interferon-γ antagonists, somatostatin, calcium channel peptide, opiate agonists such as E-2078 and dynorphin A, opiate antagonists, sleep inducing peptide, calcitonin, PTH-releasing peptide, growth hormone releasing peptide, LHRH agonists such as buserelin, goserelin, leuprolide, LHRH antagonists, anticoagulants such as hirudin and hirudin analogs, desmopressin and desmopressin analogs, melanoma receptor blockers, captopril, oxytocin, vasopressin. Urea is a particularly preferred keratolytic agent in combination with peptides by promoting dissolution of peptide in the carrier.

According to an aspect of the invention there is provided a sprayable topical pharmaceutical or cosmetic composition comprising from 1 % by weight to 55 % or 60 % by weight, in particular from 20 % by weight to 55 % by weight, and from 35 % by weight or 40 % by weight to 50 % by weight or 55 % by weight or more of a phospholipid. The sprayable composition comprises additionally a C_2 to C_4 alcohol, a keratolytic agent, and a pharmaceutically or cosmetically active agent.

The sprayable pharmaceutical or cosmetic composition preferably consists of from 20 % by weight to 55 % by weight of a phospholipid, from 40 % by weight to 75 % by weight of a C_2 to C_4 alcohol, from 0.05 % by weight to 8 % by weight of a keratolytic agent, and from 0.001 % by weight to 6 % by

weight, more preferred from 0.05 % by weight to 4 % by weight, of a pharmaceutically or cosmetically active agent, the combined components adding up to 100 %. In the sprayable composition of the invention the upper limit of sprayability is primarily controlled by phospholipid content. While compositions with a phospholipid content of up to 55 % by weight are sprayable those with a phospholipid content of 60 % usually are not. The upper limit of sprayability may however also be influenced by the content of keratolytic agent and pharmacologically or cosmetically active agent, in particular if their combined content exceeds 3 % by weight, so as to lower the upper limit of sprayability somewhat.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises
at least 5 % by weight of a phospholipid;
at least 20 % by weight of a C_2-C_4 alcohol;
at least 0.05 % by weight a keratolytic agent; and
optionally, comprising up to 2 % by weight of water.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises from 5 % by weight to 60 % by weight of a phospholipid; from 20 % by weight to 90 % by weight of a C_2-C_4 alcohol; and from 0.05 % by weight to 15 % by weight of a keratolytic agent.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises from 10 % by weight to 55 % by weight of a phospholipid, from 30 % by weight to 85 % by weight of a C_2-C_4 alcohol; and from 0.05 % by weight to 10 % by weight of a keratolytic agent

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises from about 5, 6, 7, 8, 9 or 10 % by weight of a phospholipid.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises 5-20 % by weight of a phospholipid.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises 10-20 % by weight of a phospholipid.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises 70-90 % by weight of a C_2-C_4 alcohol.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises 0.5-8 % by weight of a keratolytic agent.

In one embodiment of the invention, said sprayable topical pharmaceutical or cosmetic composition comprises ethanol as a C_2-C_4 alcohol.

In one embodiment of the invention, said phospholipid comprises or substantially consists of phosphatidylcholine (PC).

In one embodiment of the invention, said keratolytic agent is selected from the group consisting of glycolic acid; lactic acid; malic acid; salicylic acid; allantoin; urea and sulphur.

In one embodiment of the invention, said keratolytic agent is urea.

In one embodiment of the invention, there is provided a carrier of the invention, which is stable for at least 3 months of storage, at room temperature.

According to an one aspect of the invention, the solubility of compounds of widely differing HLB-values (hydrophilic/lipophilic-balance) or LogP values (logarithm of octanol/water partition coefficient) in PC/ethanol mixtures

increases in parallel with the concentration of phospholipid. This feature is shared by the carrier of the invention and the composition of the invention.

According to one aspect of the invention, the carrier and the composition of the invention is suitable for topical treatment of human, animal or mammalian animal skin due to rapid evaporation of the alcohol.

According to one aspect of the invention, the properties of the continuous film or layer on the skin can be varied by incorporating other lipids or solvents, for example isopropylmyristate, mono-, di- and triglycerides, silicone oils or propylene glycol.

The pharmaceutical or cosmetic composition of the invention can be prepared by providing carrier of the invention; admixing pharmaceutically or cosmetically active agent to obtain a mixture; agitating the mixture, optionally under heating, until a clear liquid has been formed.

The composition of the invention can be used for topical administration, in particular by spraying, of pharmacologically or cosmetically active agent contained therein.

The pharmaceutical or cosmetic composition of the invention may be used on humans and other animals, such as mammals. Consequently, veterinary use of the compositions of the invention is included.

The invention will now be explained in more detail by reference to a number of non-limiting examples.

Materials used in the examples

Table 1. Lipids used in the Examples

Trade name	Chemical name	Supplier	CAS No.
Lipoid S75	Soybean lecithin	Lipoid	8002-43-5
Lipoid S100	Soybean lecithin	Lipoid	8002-43-5
Phospholipon 90G	Soybean lecithin	Lipoid	8002-43-5
Capmul MCM C8 EP	Medium chain monoglycerides, Glycerol monocaprylate	Abitec Corp.	26402-26-6
Isopropyl myristate (IPM)	Isopropyl myristate	Aldrich	110-27-0

Alcohols used in the examples were ethanol 99.9% ("EtOH", VWR), 2-propanol (isopropanol, HPLC grade, Rathburn), and 2-butanol (ReagentPlus®, Sigma-Aldrich).The silicone oil used in the examples was Cyclomethicone 5-NF (Dow Corning, decamethylcyclopentasiloxane). Peptide LL-37 was from PolyPeptide Laboratories A/S Peptide DPK-060 was from Dermagen AB and Peptide PXL-01 was from Pergamum AB. All other substances were from Sigma-Aldrich.

EXAMPLE 1

Carriers of the invention

The carriers of the invention listed in Tables 2-4 were prepared. The phospholipid was dissolved in the alcohol to the desired concentration. If necessary, the dissolution was promoted by short ultrasonication at 25-40 °C in a water bath sonicator. A pre-weighed amount of keratolytic agent was added and the mixture gently heated and ultrasonicated until a clear liquid had been formed.

Table 2. Carriers of the invention (% by weight)

Carrier #	Phospholipid	%	Alcohol	%	Keratolyic agent	%
2a	Lipoid S100	3.0	Ethanol	95.0	Urea	2.0
2b	Lipoid S100	5.0	Ethanol	94.0	Urea	1.0
2c	Lipoid S100	5.0	Ethanol	93.0	Urea	2.0
2d	Lipoid S100	10.0	Ethanol	88.0	Urea	2.0

2e	Lipoid S100	20.0	Ethanol	78.0	Urea	2.0
2f	Lipoid S100	30.0	Ethanol	68.0	Urea	2.0
2g	Lipoid S100	19.8	Ethanol	73.1	Urea Glycolic acid	5.0 2.1
2h	Lipoid S100	20.0	Ethanol	75.0	Urea	5.0
2i	Lipoid S100	20.2	Ethanol	74.9	Lactic acid	4.9
2j	Lipoid S100	20.2	Ethanol	74.9	Salicylic acid	4.9
2k	Lipoid S75	4.0	2-propanol	89.0	Urea Lactic acid	2.0 5.0

Table 3. Carriers of the invention with a high phospholipid content (% by weight)

Carrier #	Phospholipid	%	Alcohol	%	Keratolytic agent	%
3a	Lipoid S100	48.0	Ethanol	48.0	Urea	4.0
3b	Lipoid S75	48.0	Ethanol	48.0	Urea	4.0
3c	Lipoid S100	48.0	2-Propanol	48.0	Urea	4.0
3d	Lipoid S100	47.0	Ethanol	47.0	Lactic acid	6.0
3e	Lipoid S100	49.5	Ethanol	49.5	Sodium lactate	1.0
3f	Lipoid S100	47.5	Ethanol	47.5	Glycolic acid	5.0
3g	Lipoid S100	48.5	2-Butanol	49.3	Salicylic acid	2.2
3h	Lipoid S75	30.1	Ethanol	68.1	Allantoin Water	0.05 1.7
3i	Lipoid S75	48.6	Ethanol	46.0	Salicylic acid	5.4
3j	Lipoid S100	49.5	Ethanol	49.5	Urea	1.0

Table 4. Carriers of the invention with additional lipid or solvent (% by weight)

Carrier #	Phospholipid	%	Alcohol	%	Keratolytic agent	%	Additional component	%
4:1	Lipoid S-100	24.5	Ethanol	47.3	Urea	4.7	MCM	23.5
4:2	Lipoid S-100	9.5	Ethanol	77.7	Urea	3.3	MCM/IPM 1:1	9.4
4:3	Phospholipon 90G	10.0	Ethanol	74.9	Urea	5.0	MCM/IPM 1:1	10.0
4:4	Lipoid S-75	29.8	Ethanol	45.8	Urea	3.5	MCM/IPM 1:1	20.9
4:5	Lipoid S-100	29.7	Ethanol	45.9	Urea	4.2	MCM/IPM 1:1	20.3
4:6	Lipoid S-100	30.0	2-Propanol Ethanol	10.0 35.3	Urea	4.6	MCM/IPM 1:1	20.1
4:7	Lipoid S-100	9.6	Ethanol	79.4	Lactic acid	1.5	MCM/IPM 1:1	9.5
4:8	Lipoid S-100	25.1	Ethanol	39.1	Lactic acid	6.0	MCM/IPM 1:1	29.8
4:9	Lipoid S-100	30.5	Ethanol	48.7	Sodium lactate	1.1	MCM/IPM 1:1	19.7
4:10	Lipoid S-100	28.9	Ethanol	43.5	Glycolic acid	4.8	MCM/IPM 1:1	22.8
4:11	Lipoid S-100	9.9	Ethanol	79.6	Salicylic acid	0.5	MCM/IPM 1:1	10.0
4:12	Lipoid S-100	29.5	2-Butanol Ethanol	10.0 37.9	Salicylic acid	2.1	MCM/IPM 1:1	20.6
4:13	Lipoid S-100	9.5	Ethanol	76.1	Urea	3.2	MCM/IPM 1:1	9.5

					Lactic acid	1.7	
4:14	Lipoid S-100	10.0	Ethanol	73.2	Urea Glycolic acid	4.8 2.1	MCM/IPM 1:1 10.0
4:15	Lipoid S-100	14.9	Ethanol	73.8	Urea Glycolic acid	5.1 1.0	MCM/IPM 1:1 5.1
4:16	Lipoid S-100	3.0	Ethanol	82.0	Urea	5.0	Propylene glycol 10.0
4:17	Lipoid S-100	4.8	Ethanol	69.9	Urea	4.8	Propylene glycol 20.4
4:18	Phospholipon 90G	5.1	Ethanol	74.8	Urea	5.0	Propylene glycol 15.2
4:19	Lipoid S-100	9.6	Ethanol	65.6	Urea	5.0	Propylene glycol 19.8
4:20	Lipoid S-100	18.7	Ethanol	57.0	Urea	5.0	Propylene glycol 19.4
4:21	Lipoid S-100	20.0	Ethanol	75.0	Urea	2.5	Propylene glycol 2.5
4:22	Lipoid S-100	20.4	Ethanol	74.7	Urea	2.5	Propylene glycol 2.4
4:23	Lipoid S-100	11.2	Ethanol	27.2	Salicylic acid	1.6	Cyclomethicone 5-NF 50.6 MCM/IPM 1:1 9.5

EXAMPLE 2

Composition of the invention

Examples of the composition of the invention are listed in Tables 5, 6 and 7. They were prepared by adding a pre-weighed amount of the respective cosmetic or pharmacologically active agent to one of the carriers of Example 1. The mixtures were gently heated and ultrasonicated until clear liquids had been formed.

Table 5. Compositions of the invention

Composition #	Carrier #	% By weight	Active agent	% By weight
5:1	2a	95.3	Diclofenac sodium	4.7
5:2	2b	95.3	Ibuprofen	4.7
5:3	2c	98.0	Ketoprofen	2.0
5:4	2d	97.8	Naproxen	2.2
5:5	2e	99.6	Cyclosporin A	0.4
5:6		98.5	Calcium pantothenate	1.5
5:7	2f	99.0	Capsaicin	1.0
5:8	2g	98.8	Retinol	1.2
5:9	2h	99.0	Clindamycin hydrochloride	1.0
5:10		91,9	Lauric acid	8.1
5:11		98.0	Sodium fusidate	2.0
5:12		99.7	Curcumin	0.3
5:13		99.1	Tacrolimus	0.9
5:14		99.9	Mometasone furoate	0.10

5:15	2i	98.5	Diclofenac Sodium	1.5
5:16	2j	99.6	Naproxen	0.4
5:17	2k	99.6	Ketoprofen	0.4

Table 6. Compositions of the invention with a high phospholipid content (% by weight)

Composition #	Carrier #	% By weight	Active agent	% By weight
6:1	3a	99.9	Betamethasone dipropionate	0.1
6:2		99.995	Calcipotriol	0.005
6:3		95.6	Diclofenac sodium	4.4
6:4		99.72	Mupirocin	0.28
6:5		98.0	Peptide LL-37	2.0
6:6	3b	99.4	Benzalkonium chloride	0.6
6:7		99.0	Benzoyl peroxide	1.0
6:8		99.8	Betamethasone valerate	0.2
6:9		99.1	Chlorhexidine	0.9
6:10		98.2	Econazole nitrate	1.8
6:11		98.7	Hydrocortisone	1.3
6:12		99.1	Hydrocortisone butyrate	0.9
6:13		98.7	Peptide DPK-060	1.3
6:14		99.5	Peptide PXL-01	0.5
6:15		99.0	Oxytocin acetate	1.0
6:16	3c	98.4	Hydrocortisone	1.6
6:17		98.0	Diclofenac sodium	2.0
6:18		98.9	Oxytocin acetate	1.1
6:19	3d	99.0	Estradiol	1.0
6:20		97.2	Diclofenac sodium	2.8
6:21		99.0	Peptide DPK-060	1.0
6:22		98.7	Peptide LL-37	1.3
6:23	3e	96.3	Diclofenac sodium	3.7
6:24		98.9	Estradiol	1.1
6:25	3f	98.8	Estradiol	1.2
6:26		99.4	Peptide PXL-01	0.6
6:27	3g	99.0	Estradiol	1.0
6:28	3h	99.0	Diclofenac sodium	1.0

Table 7. Compositions of the invention with additional lipid or solvent (% by weight)

Composition #	Carrier #	% By weight	Active agent	% By weight
7:1	4:1	99.0	Diclofenac sodium	1.0
7:2	4:2	99.7	Curcumin	0.3
7:3	4:3	99.0	Hydrocortisone	1.0
7:4	4:7	99.7	Curcumin	0.3
7:5	4:12	92.0	Lauric acid	8.0
7:6	4:13	99.7	Curcumin	0.3
7:7	4:23	99.1	Terbinafine hydrochloride	0.99

EXAMPLE 3

Comparative test 1 - anesthesia

A composition of the invention comprising anaesthetic agent was compared in respect of onset of action of active agent with a corresponding composition lacking keratolytic agent (Table 8).

Table 8. Comparative test in respect of onset of action of active agent

Component	Composition A % by weight	Composition B* % by weight
Phospholipid (Lipoid S75)	41.4	43.7
Absolute ethanol	45.1	47.0
Urea	5.2	0
Lidocaine (active agent)	4.4	4.6
Prilocaine (active agent)	3.9	4.1

* Composition not comprised by the invention.

The compositions were prepared by the method of Examples 1 and 2. The compositions A and B (10 µl each) were applied on the right and left volar forearms, respectively, of a male subject so as to cover skin areas of about 1 cm^2. Ten min after application a slight numbness was felt on the right forearm area but not on the left forearm area. This indicates a faster onset of action of composition A.

EXAMPLE 4

Comparative test 2 - vasodilation

Skin color measurements were used to study the onset time of methyl nicotinate induced erythema of different compositions according to methods known in the art (Bonina F P et al., *In vitro and in vivo evaluation of polyoxyethylene esters as dermal prodrugs of ketoprofen, naproxen and diclofenac*. Europ J Pharm Sci 14 (2001) 123-134; Duval C et al., *Difference among moisturizers in affecting skin susceptibility to hexyl nicotinate, measured as time to increase skin blood flow*. Skin Res Techn 9 (2003) 59-63; Wiren K et al., *Enhancement of bioavailability by lowering of fat content in topical formulations*. Br J Dermat 160 (2009) 552-556). Three formulations containing methyl nicotinate were applied to areas on the skin of both volar forearms of a male subject (age 56). Skin color was measured by using DSM II Colormeter (Cortex Technology, Denmark) which is based on an active color detecting chip where illumination is provided by white LEDs.The measured parameter (erythema index, E.I.) corresponds to the redness of the skin (Bonina F P et al., *supra*). The erythema effect (ΔE.I.) was calculated as the difference between the measured E.I and the baseline, and the onset time as the time needed to reach 75% of the maximum erythema effect after application. The figures shown in Table 9 are mean values from four treatments, after application of 6 µl of the compositions on circular test areas of 3 cm^2. The results show that adding keratolytic agents to a phospholipid containing composition shortens the onset time of methyl nicotinate induced erythema.

Table 9. Onset time of methyl nicotinate induced erythema by various compositions

Compo-sition #	Lipoid S100 (% w/w)	Ethanol (% w/w)	Keratolytic agent	% w/w)	Methyl nicotinate (% w/w)	Onset time (min)
9:1*	25.3	74.3	-	-	0.4	9.9
9:2	25.2	68.9	Urea	5.5	0.4	8.3
9:3	25.1	69.5	Glycolic acid	5.0	0.4	8.9

* Composition not comprised by the invention

EXAMPLE 5

Comparative test 3 - vasodilation

A composition of the invention comprising vasodilating agent was compared in respect of duration of action of active agent with a corresponding composition lacking keratolytic agent (Table 10).

Table 10. Comparative test in respect of duration of action of active agent

Component	Composition A of the invention % by weight	Composition B % by weight
Phospholipid (Lipoid S100)	47.5	47.5
Absolute ethanol	47.5	47.5
Urea	5.0	0
Methyl nicotinate (active agent)	0.1	0.1

The compositions were prepared by the method of Examples 1 and 2. The compositions A and B (10 µl each) were applied on the inside forearms of a male subject. Each application covered a skin area of about 1 cm^2. 15 min after application redness of the same intensities appeared on the application spots. After approximately 1 hour redness caused by composition B had faded while that caused by composition A had not. The longer duration of action of composition A indicates a better penetration into the skin than of composition B.

EXAMPLE 6

Comparative test 4 – tape stripping of curcumin treated skin

Skin color measurements were used to study the penetration of curcumin into the skin. Two formulations containing curcumin were applied to areas on the skin of the left volar forearm of a male subject (age 56). After application the test area was stripped with adhesive tape ten times. Skin color was measured using the same instrument as in Example 4. The measured quantity, the b* parameter in the CIE 1976 (L*, a*, b*) color space, was found to have a linear relationship with the amount of curcumin absorbed by the skin. The relative

amount of curcumin in the skin was calculated as the difference between the measured b* and the baseline (Δb*) after ten tape strippings, divided by the difference measured immediately after application. The numbers shown in Table 11 are mean values from two treatments, after application of 5 µl of the compositions on circular test areas of 3 cm^2.

The results indicate that adding keratolytic agents to a phospholipid containing composition enhances the penetration of curcumin into the skin.

Table 11. Relative amount remaining in the skin after application of various curcumin compositions and ten subsequent strippings by adhesive tape.

Compo-sition #	Lipoid S100 (% w/w)	Ethanol (% w/w)	IPM+MCM 1:1 (% w/w)	Urea (% w/w)	Curcumin (% w/w)	Rel. Amount curcumin after stripping
11:1*	9.5	80.7	9.4	-	0.3	0.36
11:2	9.5	77.5	9.4	3.3	0.3	0.46

* Composition not comprised by the invention

EXAMPLE 7

Antifungal composition

By the method of Example 1, carrier of the invention was prepared from 39.5 parts by weight of phospholipid (Lipoid S75), 53.1 parts by weight of absolute ethanol and 6.5 parts by weight of urea. One part by weight of terbinafine hydrochloride (active agent) was added to the carrier and the mixture gently heated and ultrasonicated until a clear liquid had been formed.

EXAMPLE 8

Antiperspirant composition

By the method of Example 1 carrier of the invention was prepared from 47.9 parts by weight of phospholipid, 47.9 parts by weight of absolute ethanol and 3.9 parts by weight of urea. Aluminum chloride hexahydrate (0.3 parts by weight, active agent) was added to the carrier and the mixture gently heated and ultrasonicated until a clear liquid had been formed.

EXAMPLE 9

Increase of solubility of active agent in a carrier by raising the carrier phospholipid content

The dissolution capacity of different carriers was tested by admixing controlled amounts of active agent. The results are listed in Table 12. The results show that increasing concentration of phospholipids in the carrier increases the dissolution capacity for substances in a wide range of polarity.

Table 12. Comparison of carrier dissolution capacity. Amount of active agent in % by weight

Tested substance	HLB*	LogP**	Carrier (%w/w) Lipoid S100	Urea	Ethanol	Tested composition (% w/w) Lowest incomplete dissolution	Highest complete dissolution
Sucrose ester	2	7-10	5.0	1.0	94.0	0.14	
			49.5	1.0	49.5		0.18
Sucrose ester	6	4-7	5.0	1.0	94.0	0.50	
			49.5	1.0	49.5		3.35
			0.0	2.0	98.0	0.65	0.59
			5.0	2.0	93.0	1.10	0.83
			10.0	2.0	88.0	0.98	0.87
			20.0	2.0	78.0	1.45	1.22
Sucrose ester	11	2-4	5.0	1.0	94.0	9.90	
			49.5	1.0	49.5		16.83
Hydrocortisone		1.6	5.0	1.0	94.0	2.28	
			49.5	1.0	49.5		2.89
			0.0	2.0	98.0	2.25	2.09
			5.0	2.0	93.0	2.37	2.22
			10.0	2.0	88.0	2.83	2.48
			20.0	2.0	78.0	3.22	2.82
			30.0	2.0	68.0	3.50	3.19
Calcium pantothenate		-1.1	0.0	2.0	98.0	0.40	0.27
			3.4	2.0	94.7		0.41
			5.0	2.0	93.0		0.50
			10.0	2.0	88.0		0.98
			20.0	2.0	78.0		1.81
			30.0	2.0	68.0		3.17

*HLB: Hydrophilic-lipophilic balance

**LogP (logarithm of octanol-water partition coefficient): Experimental value for hydrocortisone. Estimated value for calcium pantothenate. Rough estimates from theoretical calculations on average structures for sucrose esters.

EXAMPLE 10

Physical and chemical stability of carriers and compositions

The carriers 4:14 and 4:15 were analyzed for content of urea and degradation products after 4 months at 30 °C by HPLC and NMR spectroscopy. The measured remaining concentration of urea was 100 %, 97 % and 95 %, respectively, and no formation of degradation products could be detected in any of the compositions.

The topical pharmaceutical composition 7:7 and the antifungal composition from Example 7 were analyzed for content of terbinafine hydrochloride after approximately 15 months at room temperature by HPLC. The measured remaining content was 95 % and 100 %, respectively.

Composition 7:7 was also analyzed for content of salicylic acid after 15 months at 30 °C. The measured remaining content was 104 %.

The composition from Example 7 was analyzed for content of urea and degradation products after 15 months at room temperature by HPLC and NMR spectroscopy. No decrease in urea concentration and no formation of degradation products could be detected.

The topical pharmaceutical composition 6:3 was analyzed for content of diclofenac sodium by HPLC after 11 months at room temperature. No decrease in diclofenac sodium content could be detected

The results show that the carriers and compositions of the invention have a surprisingly good physical stability, as well as chemical stability for both the keratolytic agent and the incorporated active substance.

Claims

1. Topical pharmaceutical or cosmetic composition comprising a pharmaceutical or cosmetic carrier comprising
at least 3 % by weight of a phospholipid;
at least 20 % by weight of a C_2-C_4 alcohol;
at least 0.05 % by weight of a keratolytic agent; up to 2 % by weight of water; and a pharmacologically or cosmetically active agent dissolved in said carrier.

2. The composition of claim 1, comprising from 3 % by weight to 60 % by weight of the phospholipid; from 20 % by weight to 90 % by weight of the C_2-C_4 alcohol; from 0.05 % by weight to 15 % by weight of the keratolytic agent; from 0.001 % by weight to 8 % by weight of the pharmacologically or cosmetically active agent; and water up to 2 % by weight; wherein the components are added up to a total of 100% by weight.

3. The composition of claim 1, comprising from 5 % by weight to 55 % by weight of the phospholipid, from 30 % by weight to 85 % by weight of the C_2-C_4 alcohol; from 0.05 % by weight to 10 % by weight of the keratolytic agent; from 0.001 % by weight to 8 % by weight of the pharmacologically or cosmetically active agent; and water up to 2 % by weight; wherein the components are added up to a total of 100% by weight.

4. The composition according to any one of claims 1 to 3, comprising 5-20 % by weight of the phospholipid.

5. The composition according to any one of claims 1 to 4, comprising 10-20 % by weight of the phospholipid.

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6. The composition according to any one of claims 1 to 5, comprising 70-90 % by weight of the C_2-C_4 alcohol.

7. The composition according to any one of claims 1 to 6, comprising 0.5-8 % by weight of the keratolytic agent.

8. The composition according to any one of claims 1 to 7, wherein said C_2-C_4 alcohol is ethanol.

9. The composition according to any one of claims 1 to 8, wherein said phospholipid comprises or substantially consists of phosphatidylcholine (PC).

10. The composition according to any one of claims 1 to 9, wherein said keratolytic agent is selected from the group consisting of glycolic acid; lactic acid; malic acid; salicylic acid; allantoin; urea and sulphur.

11. The composition of claim 10, wherein said keratolytic agent is urea.

12. The composition according to any one of claims 1 to 11, wherein said pharmacologically active agent is selected from 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; analgesic; antiulcer agent; local anaesthetic and immune response modifying agent.

13. The composition according to any one of claims 1 to 12, wherein said pharmacologically active agent is a peptide.

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14. The composition according to any one of claims 1 to 13, wherein said cosmetically active agent is selected from an antiperspirant; an antisudoral agent; an antidandruff agent; a glidant and a moisturizing agent.

15. The composition according to any one of claims 1 to 14, wherein said composition is stable for at least 3 months of storage, at room temperature.

16. The composition according to any one of claims 1 to 15, said composition being in sprayable form.

17. Topical pharmaceutical or cosmetic carrier comprising a phospholipid, a C_2-C_4 alcohol, and a keratolytic agent, the carrier comprising of
at least 5 % by weight of a phospholipid;
at least 20 % by weight of a C_2-C_4 alcohol;
at least 0.05 % by weight of a keratolytic agent; and
up to 2 % by weight of water.

18. The carrier of claim 17, comprising from 5 % by weight to 60 % by weight of the phospholipid; from 20 % by weight to 90 % by weight of the C_2-C_4 alcohol; and from 0.05 % by weight to 15 % by weight of the keratolytic agent.

19. The carrier of claim 17 or 18, comprising from 10 % by weight to 55 % by weight of the phospholipid, from 30 % by weight to 85 % by weight of the C_2-C_4 alcohol; and from 0.05 % by weight to 10 % by weight of the keratolytic agent.

20. The carrier according to any one of claims 17 to 19, comprising 5-20 % by weight of the phospholipid.

21. The carrier according to any one of claims 17 to 20, comprising 10-20 % by weight of the phospholipid.

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22. The carrier according to any one of claims 17 to 21, comprising 70-90 % by weight of the C_2-C_4 alcohol.

23. The carrier according to any one of claims 17 to 22, comprising 0.5-8 % by weight of the keratolytic agent.

24. The carrier according to any one of claims 17 to 23, wherein said C_2-C_4 alcohol is ethanol.

25. The carrier according to any one of claims 17 to 24, wherein said phospholipid comprises or substantially consists of phosphatidylcholine (PC).

26. The carrier according to any one of claims 17 to 25, wherein said keratolytic agent is selected from the group consisting of glycolic acid; lactic acid; malic acid; salicylic acid; allantoin; urea and sulphur.

27. The carrier of claim 26, wherein said keratolytic agent is urea.

28. The carrier according to any one of claims 17 to 27, wherein said carrier is stable for at least 3 months of storage, at room temperature.

29. A method of preparing a topical pharmaceutical or cosmetic composition according to any one of claims 1 to 16 comprising:
(a) providing carrier according to any one of claims 17 to 28;
(b) admixing a pharmaceutically or cosmetically active agent;
(c) agitating said mixture obtained in step (b), optionally under heating, until a clear liquid has been formed.

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30. Use of a topical pharmaceutical composition according to any one of claims 1 to 16, for administration of pharmacologically active agent contained therein.

31. The use of claim 30, wherein said administration is by spraying.

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