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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 January 2014 (09.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/006201 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 9/70* (2006.01)
A61K 9/12 (2006.01)

(21) International Application Number:
PCT/EP2013/064300

(22) International Filing Date:
5 July 2013 (05.07.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/668,846 6 July 2012 (06.07.2012) US

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

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

(54) Title: A TOPICAL COMPOSITION COMPRISING A FILM-FORMING POLYMER FOR DELIVERING AN ACTIVE INGREDIENT TO SKIN

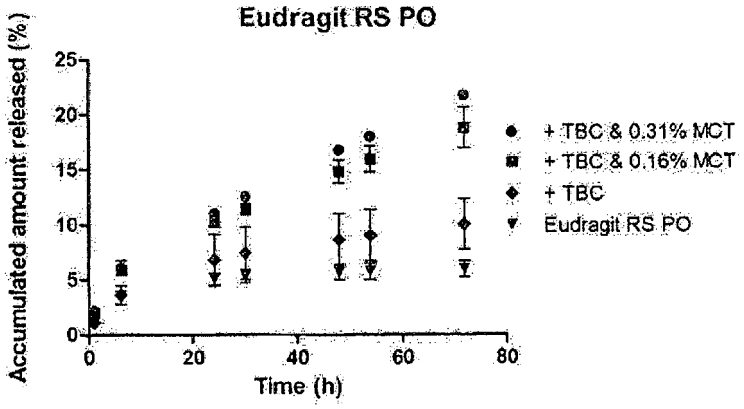


Fig. 8

(57) Abstract: A sprayable film-forming pharmaceutical composition for dermal application comprises at least one therapeutically active ingredient dissolved in a pharmaceutically acceptable propellant selected from the group consisting of dimethyl ether, diethyl ether and methylethylether, and a mixture of dimethyl ether, diethylether and methylethyl ether, and a second propellant selected from C_{3-5} alkanes, hydrofluoroalkanes, hydrochloroalkanes, fluoroalkanes and chlorofluoroalkanes, the propellant being present in an amount of 50-99.5% w/w of the composition, the composition further comprising a film-forming polymer, a plasticizer and an oily release-enhancing agent.

WO 2014/006201 A1

A TOPICAL COMPOSITION COMPRISING A FILM-FORMING POLYMER FOR DELIVERING AN ACTIVE INGREDIENT TO SKIN

FIELD OF INVENTION

The present invention relates to a sprayable pharmaceutical composition for application on skin and containing a film-forming polymer and at least one active ingredient, the composition forming a thin and transparent film on the skin on evaporation of a propellant.

BACKGROUND OF THE INVENTION

Human skin, in particular the outer layer, the stratum corneum, provides an effective barrier against penetration of microbial pathogens and toxic chemicals. While this property of skin is generally beneficial, it complicates the dermal administration of pharmaceuticals in that a large quantity, if not most, of an active ingredient applied on the skin of a patient suffering from a dermal disease may not penetrate into the viable layers of the skin where it exerts its activity. To ensure an adequate penetration of the active ingredient into the dermis and epidermis, it is generally preferred to include the active ingredient in a dissolved state, typically in the presence of a low-molecular volatile solvent such as an alcohol, e.g. ethanol, or a diol, e.g. propylene glycol, which may also act as a penetration enhancer for the active ingredient. Another way to obtain penetration of the active ingredient into the skin is to provide occlusion by formulating the acitve ingredient in a hydrophobic vehicle such as petrolatum. However, ointments containing petrolatum generally have a tacky or greasy feel that persists for quite some time after aplication, and are consequently not cosmetically acceptable.

As an alternative to conventional formulations such as ointments, compositions containing film-forming polymers in which an active ingredient has been incorporated have been developed. Film-forming compositions have mainly been used to provide transdermal delivery of an active ingredient such as in transdermal patches or, more recently, as film-forming solutions composed of a film-forming polymer, a plasticiser and a low-molecular volatile solvent for the active ingredient. When the solution is applied on skin, a thin polymeric film is formed after evaporation of the solvent.

EP 515 312 B1 discloses a topical formulation containing terbinafine as the active ingredient and a film-forming polymer, e.g. polyvinylacetate or acrylic and methacrylic acid ester copolymers, for use as a nail varnish in the treatment of onchomycosis.

WO 2006/111426 discloses a film-forming solution containing a vitamin D derivative and a corticosteroid for use as a nail varnish in the treatment of nail psoriasis. The film-forming polymer may be selected from polyvinylpyrrolidone, butyl ester of polyvinyl methyl ether and maleic acid copolymer and acrylate and ammonium methacrylate copolymer. The composition may contain ethanol as a solvent and may additionally contain a penetration enhancer.

US 2007/0248658 discloses compositions comprising film-forming polyurethanes or polyurethane and acrylate copolymers and one or more active ingredients for use in dermal or transdermal delivery of the active ingredient(s) such as ethinylestradiol. The composition may additionally contain a low-molecular volatile solvent such as ethanol or isopropanol and a penetration enhancer such as oleic acid, oleyl alcohol, propylene glycol propylene carbonate, N-methylpyrrolidone and isopropyl myristate.

US 2004/0213744 discloses a sprayable composition for topical application comprising a film-forming polymer, a permeation enhancer, a solubilizer, a plasticizer and an active ingredient. The film-forming polymer may be an acrylic polymer or copolymer, a methacrylic acid polymer or copolymer, polyvinylacetate, polyvinyl alcohol, polyvinylpyrrolidone or a cellulose polymer. The permeation enhancer may be selected from surfactants, oleic acid, mixed esters of capric and caprylic acid, polyhydric alcohols, isopropyl myristate etc. The solubilizer may be a surfactant, polyhydric alcohol or a copolymer of dimethylamine ethyl methacrylate and methacrylic acid ester copolymer. The plasticizer may be selected from triethyl citrate, dimethyl isosorbide, acetyl tributyl citrate, castor oil, propylene glycol etc. The composition may further include a propellant, e.g. hydrocarbon, hydrofluorocarbon, dimethylether, nitrogen, carbon dioxide, etc.

WO 2007/031753 discloses a film-forming composition comprising an active ingredient which is present in at least 80% saturation, a film-forming polymer such as polyvinylpyrrolidone, polyvinyl alcohol, acrylic polymers and copolymers, methacrylic polymers and copolymers and cellulose polymers, a low-molecular volatile solvent such as ethanol, a propellant such as hydrofluoroalkane, and preferably also an antinucleating agent such as polyvinyl alcohol and a plasticizer such as glycerol, polyethylene glycol, oleic acid, citric acid, fatty acid esters, hydrocarbons etc.

An object of the present invention is to provide film-forming compositions that are thin and transparent so that they form a nearly invisible film on the skin, the film being flexible, fast drying and non-sticky.

Another object of the invention is to provide film-forming compositions that are capable of releasing an active ingredient incorporated therein over a prolonged period of time into the upper layers of the skin so that the composition may be administered less frequently than conventional topical compositions such as creams, ointments or gels.

Another object of the invention is to provide a film-forming composition with improved penetration of the active ingredient incorporated therein into the upper layers of the skin, especially the stratum corneum, in the absence of conventional penetration enhancers such as alcohols or propylene glycol which are potential skin irritants. The stratum corneum may in this case function as a reservoir from which the active ingredient is gradually released.

A further object of the invention is to provide a composition in which the active ingredient will not be significantly degraded, but remains chemically and physically stable throughout the shelf-life of the composition.

SUMMARY OF THE INVENTION

Film-forming compositions disclosed in the literature suffer from the drawback that only a minor proportion of the active ingredient incorporated therein is released from the composition. In the research leading to the present invention, we have surprisingly found that if an oily component is added to the film-forming composition, it is possible to obtain increased release over time of the active ingredient from the resulting film. Thus, it may be possible to obtain extended release of the active ingredient over a period of several days and consequently omit daily applications of a topical composition, which is currently the norm. Furthermore, it may be possible to provide sufficient penetration of the active ingredient into the skin without including a conventional penetration enhancer in the composition.

Accordingly, in one aspect the present invention relates to a sprayable film-forming pharmaceutical composition for dermal application, the composition comprising at least one therapeutically active ingredient dissolved in a pharmaceutically acceptable propellant selected from the group consisting of dimethyl ether, diethyl ether and methylethyl ether, and a mixture of dimethyl ether, diethyl ether and methylethylether and a second propellant selected from C_{3-5} alkanes, hydrofluoroalkanes, hydrochloroalkanes, fluoroalkanes and chlorofluoroalkanes, the propellant being present in an amount of 50-99.5% w/w of the composition, the composition further comprising a film-forming polymer in an amount of 0.1-50% w/w, a plasticizer in an amount of 0.1-10% w/w, and an oily release-enhancing agent in an amount of 0.1-15% w/w.

Film-forming compositions of the invention have been found to form thin, transparent films when applied on skin. The compositions are virtually invisible and therefore more cosmetically acceptable to patients compared to visible patches. The film-forming compositions dry quickly and are not sticky, thus avoiding adhesion to the patients' clothing. When tested for substantivity, i.e. the ability to resist abrasion as a result of washing or general wear after application on skin, compositions including a hydrophobic film-forming polymer tend to exhibit increased substantivity on skin relative to compositions containing a hydrophilic film-forming polymer. Furthermore, the oily release-enhancing agent may act as an emollient to improve hydration of the skin and control transepidermal water loss, thus reinforcing the occlusive effect of the film-forming polymer.

In another aspect, the invention relates to a composition as disclosed herein for use in the treatment of dermal diseases and conditions.

The compositions according to the invention may be dispensed from aerosol containers, typically of the type comprising a container body and valve assembly. The container body may, for instance, comprise a metal body, preferably lined with an chemically inert coating material to avoid degradation of the composition due to interaction between the body and the composition.

The valve assembly may comprise a valve cup, sometimes referred to as a mounting cup, a valve body or housing provided with a valve stem, a spring, a dip tube and an actuator. An inner gasket typically seals a hole in the valve stem, but when the actuator is operated the valve stem is shifted so that the hole is uncovered. Once exposed, the pressure exerted by the propellant in the container body forces the composition to flow through the hole into the dip tube and the valve stem and out through the actuator. As will be understood, when the actuator is released the valve spring returns the valve stem to the position where the hole is once again sealed.

The valve stem and actuator each contain one or more holes (orifices) and channels, the number, size and shape of which are determined in conjunction with the physical properties of the particular composition formulation so as to control both the flow rate through the valve and the characteristics of the spray that emerges from the actuator.

The spray pattern and flow rate may be controlled by means of a separate insert fitted into the outlet orifice of the actuator and which provides the terminal orifice for the actuator assembly. The channel through the insert leading to the outlet typically includes a portion narrower in diameter than the channel in the body of the actuator so that fluid

emerging from the actuator channel into the insert channel is caused to swirl and break up into droplets. The insert may be profiled, for example it may be stepped, so that the composition is forced forwards and out of the terminal orifice in a forward motion, rather than the more usual rotational motion. This results in a homogeneous or solid spray pattern and hence enabling a user better to focus the composition on the area of skin being treated.

Since inhalation of the composition according to the invention is not desirable, it is preferred that the dimensions of the fluid channels, orifices, inserts, etc are selected to avoid production of a fine mist on expulsion.

The valve assembly may comprise a metering valve to permit only a metered quantity of the composition to be dispensed with each actuation of the actuator.

For storage, safety and/or hygiene reasons, the actuator may be provided with an protective hood or overcap, separate or integral therewith. The overcap may be moveable from a first position in which the terminal orifice is enclosed to a second position where the orifice is exposed; in the second position, the cover may also function as a directing nozzle by limiting the spray area. The actuator itself may comprise a simple button actuator, or may for example comprise a flip-top or twist-lock. In another arrangement, an overcap having an integral finger actuator may be secured to the container and cover an underlying actuator button. The underside of the overcap may include for example a plurality of projections for contacting the actuator button upon movement due to finger pressure of the operator and triggering the valve to open.

Alternatively, or in addition thereto, the actuator may be moveable between a first position in which the valve is prevented from being intentionally or accidentally operated and a second operative position. For example, part of the valve assembly may be rotatable about the valve stem such that in one rotary position the actuator is operable to dispense the product while in another rotary position the actuator aligns with projections or abutments on the container to prevent actuation. Such a "twist and spray" mechanism may include tactile or audible indications of the open and closed positions.

The inclusion of a tamper-evidence tab, which has to be broken before first use of the aerosol container, is desirable.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the release of betamethasone valerate (BMV) from a film-forming composition containing Klucel LF and 20% (by weight of the dry film-forming polymer) of the plasticizers TEC, TBC and DBS, or the oily release-enhancing agent MCT compared to the release of BMV from a film-forming composition containing no plasticizer or oily release-enhancing agent over a period of 72 hours.

Fig. 2 shows the release of BMV from a film-forming composition containing Eudragit RS PO and 20% (by weight of the dry film-forming polymer) of the plasticizers TEC, TBC and DBS, or the oily release-enhancing agent MCT compared to the release of BMV from a film-forming composition containing no plasticizer or oily release-enhancing agent over a period of 72 hours.

Fig. 3 shows penetration of BMV from all three test compositions in the course of 24 hours.

Fig. 4 shows the concentration of betamethasone dipropionate (BDP) and its metabolite betamethasone in the skin of hairless rats after 1 day and 7.

Fig. 5 shows the serum concentration of betamethasone over 24 h from application on the skin of hairless rats of film-forming compositions and the comparative ointment.

Figure 6a shows a cross-section of a container intended for a pressurized spray composition of the invention, comprising a container body (1) onto which is fitted a valve assembly comprising a valve cup (3), a valve body (5), an actuator (4) and a dip tube (2). As shown in this embodiment, the present composition may be a two-phase system comprising a composition phase (6) and a vapor phase (8).

Fig. 6b shows a cross-section of a container intended for a pressurized spray composition of the invention, comprising a container body (1) onto which is fitted a valve assembly comprising a valve cup (3), a valve body (5), an actuator (4) and a dip tube (2). As shown in this embodiment, the present composition may be a three-phase system comprising a vehicle phase (6), a propellant phase (7) and a vapor phase (8).

Fig. 7 shows a cross-section of a valve assembly to be mounted on the body of a container body (1), comprising a valve cup (3) provided with sealing (31) between the container body (1) and the valve cup (3) and a gasket (32), a valve body (5) provided with a valve stem (51) and a spring (53) connected to an actuator (4) provided with an

insert (44) with a terminal orifice (41) through which the composition present in the container body (1) is expelled when the actuator (4) is depressed. The valve stem (51) contains an aperture (52) through which the composition present in the container body (1) may flow when the actuator is depressed. The valve body is further provided with a tailpiece (55) to which the dip tube (2) is connected. The tailpiece (55) is provided with an aperture (54) permitting the composition to flow from the dip tube (2).

Fig. 8 is a graph showing the accumulated amount of released BDP as a function of time from film-forming compositions containing Eudragit RS PO as the film-forming polymer alone, Eudragit RS PO together with tributyl citrate as the plasticizer or Eudragit RS PO together with tributyl citrate and 0.16% w/w or 0.31% w/w MCT as the oily release-enhancing agent.

Fig. 9 is a graph showing the amount of active ingredient (BDP) in skin of hairless guinea pigs as a function of time after application of a film-forming composition containing Eudragit RS PO alone (formulation 1), Eudragit RS PO and tributyl citrate (formulation 2) and Eudragit RS PO, tributy citrate and 0.16% w/w MCT (formulation 4).

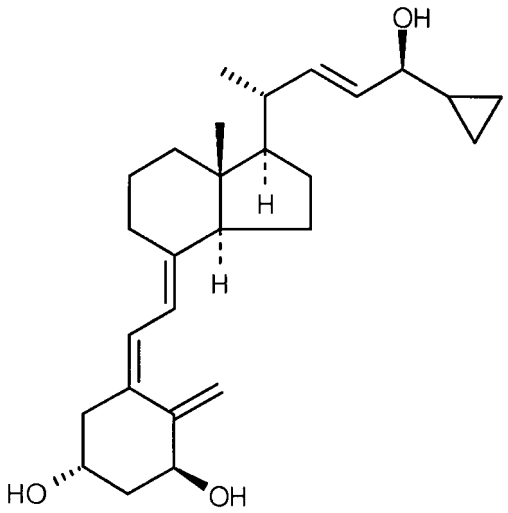
DETAILED DISCLOSURE OF THE INVENTION

Definitions

The term "vitamin D derivative" is intended to indicate a biologically active metabolite of vitamin D_3, such as calcitriol, or a precursor to such a metabolite, such as alfacalcidol.

The term "vitamin D analogue" is intended to indicate a synthetic compound comprising a vitamin D scaffold with sidechain modifications and/or modifications of the scaffold itself. The analogue exhibits a biological activity on the vitamin D receptor comparable to that of naturally occurring vitamin D compounds.

"Calcipotriol" is a vitamin D analogue of the formula



Calcipotriol has been found to exist in two crystalline forms, an anhydrate and a monohydrate. Calcipotriol monohydrate and its preparation are disclosed in WO 94/15912.

The term "storage stability" or "storage stable" is intended to indicate that the composition exhibits chemical and physical stability characteristics that permit storage of the composition for a sufficient period of time at refrigeration or, preferably, room temperature to make the composition commercially viable, such as at least 12 months, in particular at least 18 months, and preferably at least 2 years.

The term "chemical stability" or "chemically stable" is intended to mean that no more than 10%, preferably no more than 6%, of the active ingredients degrades over the shelf-life of the product, typically 2 years, at room temperature. An approximation of chemical stability at room temperature is obtained by subjecting the composition to accelerated stability studies at 40°C where the composition is placed in a heating cupboard at 40°C and samples are taken at 1, 2 and 3 months and tested for the presence of degradation products by HPLC. If less than about 10% of the substance has degraded after 3 months at 40°C, this is usually taken to correspond to a shelf-life of 2 years at room temperature. When the active ingredient included in the composition is calcipotriol, "chemical stability" usually indicates that the calcipotriol does not degrade significantly over time to 24-epi calcipotriol or other degradation products of calcipotriol in the finished pharmaceutical product.

The term "physical stability" or "physically stable" is intended to mean that the active ingredients do not precipitate from the propellant or vehicle phases throughout the shelf life of the composition.

The term "substantially anhydrous" is intended to mean that the content of free water in the ointment composition does not exceed about 2% by weight, preferably not about 1% by weight, of the composition.

The term "medium-chain triglycerides" is used to indicate triglyceride esters of fatty acids with a chain length of 6-12 carbon atoms. A currently favoured example of such medium chain triglycerides is a mixture of caprylic (C_8) and capric (C_{10}) triglycerides, e.g. available under the trade name Miglyol 812.

The term "skin penetration" is intended to mean the diffusion of the active ingredient into the different layers of the skin, i.e. the stratum corneum, epidermis and dermis.

The term "skin permeation" is intended to mean the flux of the active ingredient through the skin into the systemic circulation or the receptor fluid of the Franz cell apparatus used in the experiment.

The term "release" is intended to indicate the amount of active ingredient leaving the composition when it is applied on a surfacte, e.g. a silicone membrane. The *in vitro* release through the membrane may be determined by the method disclosed in Example 2. In this context, the term "extended release" is intended to mean that the release of the active ingredient takes place over a period of at least 48 hours, such as 72 hours. The term "increased release" is intended to indicate that the total amount of active ingredient released over time is increased from a film-forming composition containing both a plasticizer and an oily release-enhancing agent compared to a film-forming composition containing the film-forming polymer alone or together with a plasticizer, but not an oily release-enhancing agent.
The term "low-molecular volatile solvent" is used to indicate a lower alcohol such as methanol, ethanol, isopropanol or butanol, a C_{1-4} ester of a C_{1-4} carboxylic acid such as methyl acetate, ethyl acetate, butyl acetate, methyl formate or propyl propionate, or acetone.

Embodiments

In the present composition, the film-forming polymer may be selected from the group consisting of cellulose derivatives, acrylic polymers, acrylic copolymers, methacrylate polymers, methacrylate copolymers, polyurethanes, polyvinylalcohol or a derivative thereof such as polyvinylacetate, silicone polymers and silicone copolymers, or copolymers thereof.

When the film-forming polymer is a cellulose derivative, it may be selected from the group consisting of ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose.

When the film-forming polymer is an acrylic polymer, it may be selected from the group consisting of methyl methacrylate and butyl methacrylate copolymer, ethyl acrylate and methyl methacrylate copolymer, acrylate and ammonium methacrylate copolymer type A and type B, and acrylates/octylacrylamide copolymer.

In the present composition, the plasticizer may be selected from the group consisting of triethyl citrate, tributyl citrate, acetyl triethyl citrate, triacetin, dibutyl sebacate and polyethylene glycol 100-1000, such as polyethylene glycol 400.

Incorporation of a plasticizer in the film-forming composition decreases the glass transition temperature (Tg) of the film-forming polymer. Tg is an indirect indicator of film flexibility as the polymeric film is flexible at temperatures below Tg. Thus, Tg values below skin temperature indicates that the film is flexible on skin. In a specific embodiment, a decreased Tg has been obtained for film-forming compositions containing an acrylic polymer as the film-forming polymer and triethyl citrate as the plasticizer.

The oily release-enhancing agent may be selected from the group consisting of
(a) a polyoxypropylene fatty alkyl ether;
(b) an isopropyl ester of a straight or branched chain C_{10-18} alkanoic or alkenoic acid;
(c) a propylene glycol mono- or diester of a C_{8-14} fatty acid;
(d) a straight or branched C_{8-24} alkanol or alkenol;
(e) a C_{6-22} acylglyceride;
(f) N-alkylpyrrolidone or N-alkylpiperidone;and
(g) a mineral oil such as liquid paraffin.

When the oily release-enhancing agent is a polyoxypropylene fatty alkyl ether, it may be selected from the group consisting of polyoxypropylene-15-stearyl ether, polyoxypropylene-11-stearyl ether, polyoxypropylene-14-butyl ether, polyoxypropylene-10-cetyl ether or polyoxypropylene-3-myristyl ether.

When the oily release-enhancing agent is an isopropyl ester of a straight or branched chain C_{10-18} alkanoic or alkenoic acid, it may be selected from the group consisting of isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate or isopropyl monooleate.

When the oily release-enhancing agent is a propylene glycol monoester of a C_{8-14} fatty acid, it may be propylene glycol monolaurate or propylene glycol monocaprylate, and when it is a propylene glycol diester of a C_{8-14} alkanoic acid, it may be propylene glycol dipelargonate.

When the oily release-enhancing agent is a straight C_{8-24} alkanol, it may be capryl, lauryl, cetyl, stearyl, oleyl, linoelyl or myristyl alcohol, or when it is a branched C_{8-24} alkanol it may be a branched C_{18-24} alkanol such as 2-octyldodecanol.

When the oily release-enhancing agent is a C_{6-22} acylglyceride, it may be a vegetable oil, e.g. sesame oil, sunflower oil, palm kernel oil, corn oil, safflower oil, olive oil, avocado oil, jojoba oil, grape kernel oil, canola oil, wheat germ oil, almond oil, cottonseed oil, peanut oil, walnut oil or soybean oil, a highly purified vegetable oil, e.g. medium chain triglycerides (caprylic/capric triglycerides), long chain triglycerides, castor oil, caprylic monoglyceride, caprylic/capric mono- and diglycerides or caprylic/capric mono-, di- and triglycerides.

It has been found that using a pure C_{3-5} alkane such as butane as the propellant may not lead to sufficient dissolution of the active ingredient so that the active ingredient may precipitate out of the solution with time and result in crystal growth such that the composition is not physically stable for the entire shelf-life. Further, it has been found that this problem is minimized when dimethyl ether is used as the propellant on its own or even when a proportion of dimethyl ether is added to the C_{3-5} alkane to form a propellant mixture. Thus, in a currently preferred embodiment the present composition comprises dimethyl ether as the sole propellant or in admixture with a C_{3-5} alkane as the second propellant.

In the present composition, the C_{3-5} alkane is preferably selected from the group consisting of n-propane, isopropane, n-butane or isobutane. A particularly favoured C_{3-5} alkane is n-butane and/or isobutane.

In the propellant mixture, the ratio of n-butane and/or isobutane to dimethyl ether may favourably be in the range of 6:1-0:1 v/v, such as 5:1-1:2, 4:1-1:1, 4:2-1:1,4:2-4:3 or 4:3-1:1.

The present composition may if needed comprise a co-solvent which is a low-molecular volatile solvent. It is, however, currently preferred that the present composition is essentially free from a low-molecular volatile solvent due to the potentially irritative effect of such solvents when applied on skin.

The present composition may comprise a small amount of water which acts as a further plasticizer or as a co-solvent. It is, however, currently preferred that the composition is substantially anhydrous.

To reduce or delay crystallisation of the active ingredient in the applied, dry film-forming composition, it may be an advantage to include an anti-nucleating agent. The anti-nucleating agent may suitably be selected from polymers such as polyvinyl alcohol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose and carboxymethyl cellulose.

The active ingredient included in the present film-forming composition may suitably be selected from the group consisting of vitamin D derivatives or analogues, corticosteroids, phosphodiesterase 4 inhibitors, ingenol derivatives, retinoids such as adapalene, JAK inhibitors, NK-1 receptor antagonists, antibiotics such as fusidic acid or clindamycin, calcineurin inhibitors such as tacrolimus or pimecrolimus, keratolytic agents such as salicylic acid or lactic acid, non-steroidal anti-inflammatory agents and local anesthetics such as lidocain.

The vitamin D derivative or analogue may be selected from calcipotriol, calcitriol, tacalcitol, maxacalcitol, paricalcitol and alfacalcidol. A preferred vitamin D analogue which has been shown to be effective in the treatment of psoriasis is calcipotriol. Before dissolution in the propellant or co-solvent, calcipotriol may be in the form of anhydrate or monohydrate, preferably the monohydrate.

The corticosteroid may be selected from the group consisting of amcinonide, betamethasone, budenoside, clobetasol, clobetasone, cortisone, desonide, desoxycortisone, desoximethasone, dexamethasone, diflucortolon, diflorasone, flucortisone, flumethasone, flunisolide, fluocinonide, fluocinolon, fluorometholone, fluprednisolone, flurandrenolide, fluticasone, halcinonide, halobetasol, hydrocortisone, meprednisone, methylprednisone, mometasone, paramethasone, prednicarbate, prednisone, prednisolone and triamcinolone or a pharmaceutically acceptable ester or acetonide thereof. The corticosteroid may preferably be selected from betamethasone, budenoside, clobetasol, clobetasone, desoximethasone, diflucortolon, diflorasone, fluocinonide, fluocinolon, halcinonide, halobetasol, hydrocortisone, mometasone and triamcinolone or a pharmaceutically acceptable ester thereof. The corticosteroid ester may for instance be betamethasone acetate, betamethasone dipropionate, betamethasone valerate, clobetasol propionate, dexamethasone acetate, flumethasone pivalate, fluticasone propionate, hydrocortisone acetate, hydrocortisone butyrate or mometasone furoate. The acetonide may be selected from fluocinolone acetonide or

triamcinolone acetonide. The corticosteroid is preferably betamethasone dipropionate or betamethasone valerate.

In a currently favoured embodiment, the composition comprises calcipotriol or calcipotriol monohydrate as the vitamin D analogue and betamethasone valerate or betamethasone dipropionate as the corticosteroid.

The phosphodiesterase 4 inhibitor may for instance be selected from the compounds disclosed in WO 2008/077404, WO 2008/104175, WO 2008/128538 or WO 2010/069322 the disclosure of which is included herein by reference. A particularly preferred phosphodiesterase 4 inhibitor is 2-{6-[2-[2,3-dichloropyridin-4-yl)acetyl]-2,3-dimethoxyphenoxy}-N-propylacetamide.

The ingenol derivative may suitably be selected from the group consisting of ingenol-3-angelate, ingenol-5-angelate, ingenol-20-angelate, 20-O-acetyl-ingenol-3-angelate and 20-deoxy-ingenol-3-angelate. Ingenol-3-angelate, also known as ingenol-3-mebutate or PEP 005, has recently been approved in the US and EU for the treatment of actinic keratosis.

In a specific embodiment, the film-forming composition of the invention comprises a therapeutically active ingredient and

Acrylates/ammonium methacrylate copolymer	0.5-1.0% w/w
Medium chain triglycerides	0.1-0.5% w/w
Tributyl citrate	0.1-0.3% w/w
Butane	50-60% w/w
Dimethyl ether	40-50% w/w

The present composition may also comprise other components commonly used in dermal formulations, e.g. antioxidants (e.g. alpha-tocopherol), preservatives, pigments, emollients, skin soothing agents, skin healing agents and skin conditioning agents such as urea, glycerol, allantoin or bisabolol, cf. *CTFA Cosmetic Ingredients Handbook*, 2nd Ed., 1992. In a favoured embodiment, the composition may comprise an anti-irritative agent such as menthol, eucalyptol or nicotinamide.

The composition of the invention may be used in the treatment of psoriasis, sebopsoriasis, pustulosis palmoplantaris, atopic dermatitis, contact dermatitis, eczema, actinic keratosis, pruritus, ichtyosis, rosacea and acne and related skin diseases by topically administering an effective amount of a composition according to the invention to a patient in need of such treatment. Said method preferably comprises topical

administration once or twice a day of a therapeutically sufficient dosage of said composition. To that end, the composition according to the invention preferably contains about 0.0001-1% w/w of the active ingredient. It is envisaged that the present composition may advantageously be used for maintenance treatment of these dermal diseases, i.e. continued treatment after the disappearance of visible symptoms of the disease in order to delay recurrence of the symptoms. The present composition has the added advantage for the treatment of skin diseases involving dry or flaky skin, e.g. psoriasis, that the oily release-enhancing agent acts as an emollient hydrating and softening the flaky skin to give the skin a less dry appearance.

In a further aspect, the invention relates to a pressurized container adapted to dispensing a topical composition on an affected skin area, the container comprising a composition according to the invention and a valve assembly and actuator for releasing the composition in the form of a spray.

As shown in Fig. 6a and 6b, an example of a container suitable for a pressurized product may be composed of a container body (1) in which the present composition is stored, a dip tube (2), and a valve assembly comprising a valve cup (3), a valve body (5) and an actuator (4).

Typically, the container body (1) may be constructed from materials such as metal, glass, ceramics, polyester, polyethylene terephthalate (PET) or other polymer, or the like. Glass containers may be provided with a safety coating of for instance polypropylene to contain glass shards that may be formed on impact with a hard surface. Metal container bodies are currently preferred as they are better able to withstand impact and are amenable to surface coating. Stainless steel, tinplate and aluminium (i.e. aluminium or aluminium alloy, including anodised aluminium) container bodies are especially suitable materials for this purpose, with aluminium being currently preferred as it is light and not readily breakable.

Metal containers are typically lined or coated with an inert material to protect the composition from reactions with the metal, thereby preventing or substantially eliminating any degradation of the active ingredients or other components of the composition.

Inert materials include any suitable polymer, lacquer, resin or other coating treatment that creates a barrier between the container and the composition for preventing any chemical interaction between the composition and the container. Preferably the inert material is a non-metallic coating.

Known coatings for metal containers include acrylic, phenolic, polyester, epoxy and vinyl resins. However, a composition containing a vitamin D derivative or analogue, is likely to be chemically degraded under acidic conditions or in the presence of acidic reacting compounds. Moreover, corticosteroids are known to be chemically degraded under alkaline conditions or in the presence of alkaline reacting compounds. Accordingly, the container coating for use with a composition of the present invention should preferably be selected so that it exhibits no acidic or alkaline reactivity in itself, and that no acidic or alkaline reacting impurities are leached from it in the presence of the composition.

It has been found, for example, that a particular epoxyphenol resin inner lacquer was incompatible with one of the active ingredients, causing unacceptable chemical degradation of calcipotriol. Such degradation may possibly be due to the presence in the lacquer of colophonium which includes an acid group. On the other hand, the chemical stability of calcipotriol was satisfactory when a polyimide-polyamide resin was used as the inner coating.

In addition to polyimide-polyamide coatings, other materials suitable for lining the interior of the metal containers include polyamides, polyimides, polypropylene, polyethylene, fluoropolymers, including perfluoroethylenepropylene copolymer (FEP), fluororubber (FPM), ethylene-propylene diene monomer rubber (EPDM), polytetrafluoroethylene (PTFE), ethylene tetrafluoroethylene copolymer (EFTE), perfluoroalkoxyalkanes, perfluoroalkoxyalkylenes, or blends of fluoropolymers with non-fluorocarbon polymers. Fluoropolymers may, for example, be used in combination with polyimide-polyamide resins.

The container coating material may be applied as a single layer, or in multiple layers, for example allowing each layer to cure before application of a further layer. As well as shielding the composition from the metal container, the application of more than one coating may also help prevent adhesion of the active ingredients on the container walls.

For the same reasons, valve components of the container that are brought into contact with the composition are also preferably made of, or coated with, materials that do not cause degradation of the composition. For example, metal valve components such as the valve cup may be coated with anodized silver, epoxymelamine or polypropylene.

As well as inhibiting leakage from the container, especially leakage of propellant, materials used for gaskets or seals within the container should also preferably be chemically inert. For example, the container body and valve cup may be crimped together using an intermediate gasket which at least in part is exposed to contact with

the composition, thus if the gasket is not made of inert material it may over time result in degradation of the composition.

Extensive testing of materials used for gaskets in conventional aerosol container valves has established that polymeric materials prepared by vulcanization using sulphur-containing accelerators (e.g. thiazoles) are not suitable as gasket materials for containers intended to include the present composition, probably due to reactivity of sulphur-containing residues or impurities with one or both of the active ingredients resulting in chemical degradation.

Similarly, gasket materials permeable to the propellants included in the present composition are not suitable as gasket materials for the present purpose.

Suitable gasket or seal materials for use with compositions according the invention include fluoroelastomers (e.g. Viton V 600), fluorinated ethylene-propylene copolymer (FEP), fluororubber (FPM, e.g. VI500) or ethylene-propylene diene monomer rubber (EPDM).

Suitable materials for the dip tube have been found to be e.g. polyethylene and polypropylene. Suitable materials for the valve stem have been found to be e.g. polyamide and acetal (POM).

In the embodiment shown in Fig. 6b, the composition comprises a vehicle phase (6) , a propellant phase (7) and a vapor phase (8). In this embodiment the spray container should be shaken thoroughly before use so that the vehicle phase (6) will be homogenously suspended in the propellant phase (7).

As shown in Fig. 7, the valve assembly may be composed of a valve cup (3), which is typically made of metal such as aluminium, attached to the container body (1) by crimping, a valve body (5) which contains a valve stem (51) and a spring (53) connected to the actuator (4) which is depressed for activation to expel the composition from the container. The valve stem (51) contains at least one aperture (52) with a diameter of 0.05-1 mm through which the composition present in the container may flow when the actuator (4) is depressed. The valve stem aperture (52) may preferably be provided with a ball which allows the container to be used in different positions such as upside down or sideways .

The actuator (4) is provided with an insert (44) having a terminal orifice (41) with a diameter of 0.3-1.5 mm through which the composition is expelled. The actuator (4)

should be designed so as to provide an aerosol spray from the orifice (41) with droplets of a size sufficiently small to ensure a uniform spray of the product, yet sufficiently large to ensure that the droplets of composition do not form a fine mist on expulsion from the container such that droplets containing biologically active substances may be accidentally inhaled.

The dimensions of the insert orifice (41) and valve stem aperture(s) (52) as well as the pressure within the container generally determine the width of the spray cone formed when the composition is expelled from the aperture (4) and consequently the size of the area that will be covered by the sprayed composition.

In a particular embodiment, the container may be provided with means for metering a dose of the composition.

The invention is further illustrated by the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

Example 1

Compositions

Reference compositions were prepared including the following ingredients.

Polymer	Plasticizer				Oil	Solvent
	TEC	TBC	DBS	PEG	MCT	Ethanol
Klucel LF 5%	X	X	X	X	X	X
Eudragit E 15%	X					X
Eudragit RS 15%	X	X	X	X		X
Dermacryl 79 10%	X				X	X
Dermacryl 79 + Klucel LF					X	X

TEC: triethyl citrate

TBC: tributyl citrate

DBS: dibutyl sebacate

PEG: polyehtylene glycol 400

MCT: medium chain triglycerides

The content of plasticizer and/or oil in the compositions was 20% by weight of the dry film-forming polymer. In addition, 1.2% by weight of betamethasone valerate (1% by weight betamethasone) was added to the compositions.

To prepare the vehicle, the plasticizer/oil was dissolved in the solvent by stirring for 1-2 hours. The film-forming polymer was added slowly with stirring, and the resulting mixture was stirred overnight to complete the dissolution of the polymer.

Example 2

Compositions

Ingredients (mg/g)	01	02	03	04	05	06
Eudragit RS PO	7.8	7.8	7.8	7.8	7.8	7.8
Tributyl citrate		1.6	0.0	1.6	1.6	0.0
Medium chain triglycerides			1.6	1.6	3.1	3.1
BDP	1.6	1.6	1.6	1.6	1.6	1.6
Butane	531.8	531.0	531.0	530.2	529.3	530.2
Dimethyl ether	458.8	458.1	458.1	457.4	456.7	457.4

To prepare a sprayable film-forming composition, the active ingredient, plasticizer, oil and optionally other excipients were weighed into spray containers that were closed by inserting valve and crimping. Dimethyl ether and butane was added through the valve, and the containers were shaken to dissolve the ingredients in the propellant mixture.

Example 3

In vitro release testing of compositions of Example 1

The purpose of the study is to explore the effect of polymer and plasticizer or oily release-enhancing agent on the *in vitro* release of Betamethasone-17-valerate (BMV) from compositions according to Example 1, with a view to optimising the type and concentration of polymer and plasticizer with regard to obtaining a prolonged release profile. This is done by testing various types and concentrations of polymers and plasticizers, as these are parameters expected to affect drug release from the polymeric *in situ* forming films.

Membrane:

Dow Corning® 7-4107 Silicone Elastomer Membrane, 75µm.

Diffusion cell system:
Modified dialysis cells (LEO Pharma, Denmark).

Receptor compartment: ~1.5 ml. The actual volume of each cell is registered by weighing of the assembled cell before and after filling of the receptor compartment. Diameter: ~1.55 cm, corresponding to an available diffusion area of 1.89 cm^2.

Sheets of silicone membrane are cut to size (circles, Ø = 22mm). The membrane is placed between the two compartments of the dialysis cells with the glossy side facing the donor compartment.

The receptor compartment is filled with preheated receptor medium (the actual volume of each cell is registered by weighing) and possible air bubbles removed. The sampling arm is sealed with a plastic bung and/or parafilm to prevent evaporation of the receptor medium. Uniform mixing of the receptor phase is obtained with a magnetic bar placed in the receptor compartment. The diffusion cells are placed in a heating cabinet set at ~37°C to maintain a temperature of ~32°C at the membrane surface. The stirring bed is set at 300 rpm. The cells are allowed to equilibrate for minimum 30 min before application of FFS and thus start of experiment.

Receptor medium:
10% w/w methyl-β-cyclodextrin in 0.1M acetate buffer pH 4.5. The receptor medium is degassed in an ultrasound water bath for 20 minutes prior to the start of the experiment and before 24h and 48h sampling. It was ensured that sink conditions were present at all times during the study period; i.e. that the concentration of the drug compounds in the recipient phase was below 10% of the solubility of the drug substances in the medium.

Application, occlusion, dosage and volume of test formulation:
240µl film-forming composition (FFC) is gently applied and distributed on the membrane surface (t = 0 h) using an eppendorf pipette. The pipette is not tared before application as previous experiments showed no significant retention of formulation. This may partly be a consequence of solvent evaporation complicating the registration of possible formulation retention. The weight of 240µl FFC is registered to be used in the data processing of the release results The volume of FFC delivered by an eppendorf pipette may vary as a consequence of the varying viscosity of the FFC. Therefore, the weight of 10 consecutive applications of 240µl FFC (the corresponding placebo formulation is used for this purpose) is registered, an average calculated and used in the data processing of the release results.

After application of FFC the dialysis cell is placed back on the stirring bed. The cell is placed with the membrane horizontally to obtain an even distribution of FFC during solvent evaporation/film formation by hindering of accumulation of the FFC/film in the bottom of the donor compartment.

Exposure and sampling times:

Samples of 1500µl (the actual volume is weighed and registered) are withdrawn from each cell at regular time intervals. After each sampling the receptor compartment is refilled with preheated fresh receptor medium. The withdrawn samples are stored in sealed HPLC vials at 2-8°C and protected from light until quantification by HPLC analysis. Sampling time points: 0, 1, 6, 24, 30, 48, 54, 72h.

Study design:

Each formulation is tested in 3 replicates (n = 3).

HPLC analysis:

HPLC analysis in New Products, Analytical department according to protocol 130-FKFT-20110614A.

Data analysis:

The analytically determined BMV assay values were correspondingly corrected for the replenishments. The drug concentrations are transferred to a spread sheet (Excel) to calculate the cumulative amount released over the period of 0 to 72 h. The release rate is calculated from the linear part of the curve of the cumulative amount released versus square root of time. Based on the data of all individual cells in a group, the mean value and the standard deviation (SD) are calculated for each group.

Results

The results appear from figures 1 and 2.

Fig. 1 shows the release of BMV from a film-forming composition containing Klucel LF and 20% (by weight of the dry film-forming polymer) of the plasticizers TEC, TBC and DBS, or the oily release-enhancing agent MCT compared to the release of BMV from a film-forming composition containing no plasticizer or oily release-enhancing agent over a period of 72 hours. It appears from Fig. 1 that the inclusion of a plasticizer or oily release-enhancing agent results in a significant increase in the release of active ingredient from the film.

Fig. 2 shows the release of BMV from a film-forming composition containing Eudragit RS PO and 20% (by weight of the dry film-forming polymer) of the plasticizers TEC, TBC and DBS, or the oily release-enhancing agent MCT compared to the release of BMV from a film-forming composition containing no plasticizer or oily release-enhancing agent over a period of 72 hours. It appears from Fig. 2 that the inclusion of a plasticizer or oily release-enhancing agent results in a significant increase in the release of active ingredient from the film.

Example 4

In vitro release testing of compositions of Example 2

The purpose of the study is to explore the effect of polymer, plasticizer and oily release-enhancing agent on the *in vitro* release of BDP from compositions according to Example 2, with a view to optimising the concentration of oily release-enhancing agent with regard to obtaining a prolonged release profile.

Membrane:
Dow Corning® 7-4107 Silicone Elastomer Membrane, 75µm.

Diffusion cell system:
Modified dialysis cells (LEO Pharma, Denmark).
Receptor compartment: ~3.75 ml. The actual volume of each cell is registered by weighing of the assembled cell before and after filling of the receptor compartment.
Diameter: ~1.55 cm, corresponding to an available diffusion area of 1.89 cm^2.

Sheets of silicone membrane are cut to size (circles, Ø = 22mm). The membrane is placed between the two compartments of the dialysis cells with the glossy side facing the donor compartment.

The formulation is sprayed directly onto the membrane by pressing the actuator 10 times.

The receptor compartment is filled with preheated and degassed receptor medium (the actual volume of each cell is registered by weighing) and possible air bubbles removed. The sampling arm is sealed with a plastic bung and parafilm to prevent evaporation of the receptor medium. Uniform mixing of the receptor phase is obtained with a magnetic bar placed in the receptor compartment. The diffusion cells are placed in a heating cabinet set at ~37°C to maintain a temperature of ~32°C at the membrane surface. The stirring bed is set at 300 rpm.

Receptor medium:

10% w/w methyl-β-cyclodextrin in 0.05M acetate buffer pH 4.0. The receptor medium is degassed in an ultrasound water bath for minimum 20 minutes prior to the start of the experiment and before 24h and 48h sampling. It was ensured that sink conditions were present at all times during the study period; i.e. that the concentration of the drug compounds in the recipient phase was below 10% of the solubility of the drug substances in the medium.

Composition of acetate buffer

Excipient (g/L)	**05P**	**Function**
Acetic acid, glacial	2.567	Buffer
Sodium acetate trihydrate	0.988	Buffer
Methyl-β-cyclodextrin	100	Solubilising agent
Purified water	Ad 1 L	Solvent
NaOH/HCl ad	pH 4.0	

Preparation of acetate buffer

Mix all the excipients. Adjust the pH with either NaOH or HCl to obtain a pH of 4.0. Store the buffer at 5°C until use.

Exposure and sampling times:

Samples of 1500µl (the actual volume is weighed and registered) are withdrawn from each cell at regular time intervals. After each sampling the receptor compartment is refilled (the exact same volume as withdrawn) with preheated fresh receptor medium. The withdrawn samples are stored in brown sealed HPLC vials at 2-8°C and protected from light until quantification by HPLC analysis at the end of the experiment.

Sampling time points: 0, 1, 6, 24, 30, 48, 54, 72h.

Study design:

Each formulation is tested in 3 replicates (n = 3).

Analysis of samples

Column: Sunfire C18; 3.5 µm or 5µm; 150x4.6 mm ID or equivalent

Mobile Phase: Acetonitrile/0.01 M $(NH_4)_2HPO_4$ pH 6.4, 70:30 (v/v).

Flow rate: 0.8 ml/min

Detection Wavelength: 240 nm

Injection volume: 10 µl

Column temperature:	25 °C
Rack temperature:	10 °C
Retention time BDP:	~5.8min
Runtime:	~8 min

Results

The accumulated amount of released BDP (µg/cm^2) is shown as a function of time in Figure 8. The lowest release is observed from the propellant driven spray formulation containing only the film-forming polymer. The addition of tributyl citrate has a release enhancing effect which is further increased by adding 0.16% w/w or 0.31% w/w MCT as the release-enhancing agent.

Example 5

Skin substantivity testing

Topical substantivity of compositions according to Example 1 is tested by applying film-forming compositions including a colour additive (curcumin) in an amount of 1 mg/g on excised pig ear skin and determining the ΔE value before and after the film has been washed and dried. The ΔE value is a measure of the difference in skin colour before and after washing and drying. Thus, a substantive film results in a low ΔE value, preferably close to zero.

5% Klucel LF FFS/20% MCT:

- ΔE (start → 1. Wash/dry) = 38
- ΔE (start → 2. Wash/dry) = 42

15% Eudragit RS PO FFS/20% MCT:

- ΔE (start → 1. Wash/dry) = 0.1
- ΔE (start → 2. Wash/dry) = 1.2

10% Dermacryl 79 FFS/20% MCT:

- ΔE (start → 1. Wash/dry) = 0.9
- ΔE (start → 2. Wash/dry) = 1.5

⇨ Klucel < Dermacryl ~ Eudragit

The difference in substantivity can be ascribed to the water-solubility of the film-forming polymer used in the composition → the hydrophilic Klucel film-forming composition is very easily washed off, i.e. has a very poor substantivity.

Example 6

In vitro skin penetration

To investigate the skin penetration and permeation of BMV from compositions according to example 1, a skin diffusion experiment was conducted. Full thickness skin from pig ears was used in the study. The skin was cleaned and kept frozen at -18°C before use. On the day prior to the experiment the skin was placed in a refrigerator (5±3°C) for slow defrosting.

Static Franz-type diffusion cells with an available diffusion area of 3.14 cm^2 and receptor volumes ranging from 8.6 to 11.1 ml were used in substantially the manner described by T.J. Franz, "The finite dose technique as a valid in vitro model for the study of percutaneous absorption in man", in *Current Problems in Dermatology*, 1978, J.W.H. Mall (Ed.), Karger, Basel, pp. 58-68. The specific volume was measured and registered for each cell. A magnetic bar was placed in the receptor compartment of each cell. After mounting the skin, physiological saline (35°C) was filled into each receptor chamber for hydration of the skin. The cells were placed in a thermally controlled water bath which was placed on a magnetic stirrer set at 300 rpm. The circulating water in the water baths was kept at 35±1°C resulting in a temperature of about 32°C on the skin surface. After 30 min the saline was replaced by the receptor medium, 15 mM isotonic acetate buffer, pH 5.5, containing 1% methyl-β-cyclodextrin. Sink conditions were maintained at all times during the period of the study, i.e. the concentration of the active compound in the receptor medium was below 10% of the solubility of the compound in the medium.

The *in vitro* skin permeation of each test composition containing ^{3}H-BMV was tested in 6 replicates (i.e. n=6). Each test composition was applied on the skin membrane at 0 hours using a pipette.

The skin penetration experiment was allowed to proceed for 24 hours. Samples were then collected from the following compartments at 2, 6 and 24 h (only the receptor medium was sampled at 24 h):

The remaining film was removed, and the stratum corneum was collected by tape stripping once using up to 15 D-Squame® tape discs (diameter 22 mm, CuDerm Corp., Dallas, Texas, USA). Each tape disc is applied to the test area using a standard pressure for 10 seconds and removed from the test area in one gentle, continuous move. For each repeated strip, the direction of tearing off was varied. The viable epidermis and dermis was then sampled from the skin in a similar fashion.

Samples (1 ml) of the receptor fluid remaining in the diffusion cell were collected and analysed.

The concentration of ^{3}H-BMV in the samples were determined by liquid scintillation counting.

The results appear from Figure 3 below showing that in the course of 21 hours BMV penetrated from all three test compositions, and that the BMV mainly accumulated in the stratum corneum rather than in the epidermis. More of the BMV penetrated from the Klucel LF composition containing 20% (by weight of dry film-forming polymer) MCT than from the Klucel LF composition without plasticizer or oily release-enhancing agent. None of the BMV permeated into the receptor medium.

Example 7

In vivo penetration into the skin of hairless rats

Compositions similar to those described in Example 1, but containing betamethasone dipropionate (BDP; 0.643 mg/g) as the active ingredient and Dermacryl 79 (blue), DynamX (red) and Eudragit RL PO (green) as the film-forming polymers are investigated for penetration into the skin of hairless rats over a period of 7 days. A betamethasone ointment (purple) is used as a comparative formulation.

Male hairless rats of the OFA-hr/hr strain are obtained from Charles River, USA.

The rats are weighed prior to study initiation. Under isofluorane anesthesia, 100 µl of formulation is applied to a 4x3 cm area on the back of each rat. The rat is left for 2 minutes to permit the formulation to dry, and an Optiskin film (5.3x7.2 cm, URGO Laboratories, France) is applied over the area and on top of that, Fixomull stretch (BSN Medical, Germany).

Sublingual blood samples are collected from the animals in each group to be terminated 24 h post dosing. The samples are drawn 30 min, 2 h, 4 h and 6 h post dosing.

Animals are terminated at either 24 h or 7 days post dosing. Sublingual blood samples are collected from each animal prior to termination. The rats are euthanized with CO_2. Skin biopsies are taken from the applied skin area. The skin is cleaned gently with a tissue soaked in 99.9% ethanol. The biopsies are weighed and kept at -80° until quantitative analysis.

The concentration of BDP or betamethasone in the samples is determined by LC mass spectrometry.

The results appear from Figs. 4 and 5 below.

Fig. 4 shows the skin concentration of BDP and its metabolite betamethasone after 1 day and 7 from which it appears that the skin penetration after one day is highest from a film-forming composition containing DynamX as the film-forming polymer, and that application of film-forming compositions containing DynamX or Eudragit RL PO as the film-forming polymer results in higher penetration of the active ingredient that when the comparative ointment is applied. In further appears that BDP and/or betamethasone remains in the skin for 7 days after application of a film-forming composition containing Dermacryl 79 or DynamX.

Fig. 5 shows the serum concentration of betamethasone over 24 h from application of the film-forming compositions and the comparative ointment. It appears that application of the oinment leads to permeation through the skin, whereas hardly any betamethasone is found in serum after application of the film-forming compositions.

Example 8

In vivo penetration into the skin of hairless guinea-pigs

The objective of this study is to investigate the pharmacokinetics in skin of betamethasone dipropionate over an extended period of time (7 days) after application of film-forming compositions 1, 2, 4 and 5 of Example 2 on the flank of hairless guinea-pigs.

The study was performed in 12 female IAF hairless guinea-pigs, Crl:HA-*Hr*^{hr} from Charles River. The animals were housed according to standard routines at LEO Pharma.

Prior to dosing, the animals were anaesthetized with a mixture of ketamine 50 mg/kg and xylazine 5 mg/kg i.p (1.25 ml/kg),

The compositions were applied by spraying according to the schedule below, and the dosing area was controlled by spraying through a dosing template of filter paper with a circular hole (18 mm diameter). All formulations were applied by 5 bursts of spray.

Date	Animal no.	RB Tx field	RF Tx field	LB Tx field	LF Tx field

2013-06-13	1	1	2	4	5
2013-06-13	2	5	4	2	1
2013-06-13	3	3	4	1	2
2013-06-17	4	1	2	4	5
2013-06-17	5	5	4	2	1
2013-06-17	6	4	5	1	2
2013-06-19	7	1	2	4	5
2013-06-19	8	5	4	2	1
2013-06-19	9	4	5	1	2
2013-06-20	10	1	2	4	5
2013-06-20	11	5	4	2	1
2013-06-20	12	4	5	1	2

After application of the compositions, the animals were observed regularly. Parameters observed were:

Local skin reaction at sites of administration, any behavioural signs of discomfort or irritation by the formulations, visible remains of the formulations.

The animals treated on Thursday 2013-06-20 were terminated 2 hours after treatment.

Each animal was anaesthetized with a mixture of ketamine 50 mg/kg and xylazine 5 mg/kg i.p (1.25 ml/kg), and the animals were euthanized by asphyxiation in CO_2. Each test site was gently swabbed twice with soaked cotton in order to remove any excess formulation, and one 4 mm punch biopsy was taken from each site. Subsequently the treatment sites were tape stripped 20 times using D-Squame tape. The tape strips were saved for analysis. After tape stripping one 4 mm biopsy was taken from each site. The biopsies were delivered to DMPK for analysis of tissue concentration.

Bioanalysis by LC-MS/MS was performed at DMPK&Safety. Briefly, betamethasone dipropionate was extracted from skin biopsies using ether. The ether was evaporated and the residue was reconstituted in Methanol:Water (50:50) containing deteurated betamethasone dipropionate as internal standard. Tape strips were extracted using acetonitrile.

Samples were analysed using an AB Sciex API 5000.

Results

The amount of BDP in the samples were corrected for variation in area and expressed as $\mu g/cm^2$.

In the tape strips all compositions showed higher amounts of BDP at the early time points (2h, 24h) compared to the late time point. The tape strips from the fields treated with Formulation 2 showed the highest amounts of betamethasone dipropionate.

The results from tape stripped skin are shown in Fig. 9. The skin that had been tape stripped showed low amounts of BDP, reflecting that a large proportion of the dose was residing in the tape strips. However, skin treated with Formulation 4 had a less pronounced decrease in skin amounts over time. This may indicate a prolonged release from Formulation 4 relative to the other formulations. Skin treated with Formulation 2 showed the highest amounts in the tape stripped skin after 1-3 days, but after 7 days, skin treated with Formulations 1 and 2 showed similar amounts of Betamethasone dipropionate. Due to a high variability in the analysis of samples of stripped skin treated with formulation 5, data for that formulation are not presented.

Intact skin showed higher amounts of BDP than what was observed for the tape stripped skin (data not shown). This reflected the fact that a large proportion of the dose was residing in the stratum corneum. Skin treated with Formulation 2 showed the highest amounts of compound, and skin treated with Formulations 1, 4 and 5 showed lower amounts.

The amounts of BDP in the tape strips and in the non-stripped skin were similar, reflecting the fact that most of the dose resided in the stratum corneum. Formulation 2 showed the highest amount in both sample types at the early time points.

The skin that had been tape stripped showed low amounts of BDP. Skin treated with formulation 2 showed the highest amounts in the tape stripped skin after 1-3 days, but after 7 days, skin treated with formulations 1 and 2 showed similar amounts of BDP. However, skin treated with formulation 4 had a less pronounced decrease in skin amounts as a function of time. This may indicate a prolonged release from formulation 4 relative to the other formulations.

CLAIMS

1. A sprayable film-forming pharmaceutical composition for dermal application, the composition comprising at least one therapeutically active ingredient dissolved in a pharmaceutically acceptable propellant selected from the group consisting of dimethyl ether, diethyl ether and methylethylether, and a mixture of dimethyl ether, diethylether and methylethyl ether, and a second propellant selected from C_{3-5} alkanes, hydrofluoroalkanes, hydrochloroalkanes, fluoroalkanes and chlorofluoroalkanes, the propellant being present in an amount of 50-99.5% w/w of the composition, the composition further comprising a film-forming polymer in an amount of 0.1-50% w/w, a plasticizer in an amount of 0.1-10% w/w, and an oily release-enhancing agent in an amount of 0.1-15% w/w.

2. A composition according to claim 1, wherein the film-forming polymer is selected from the group consisting of cellulose derivatives, acrylic polymers, acrylic copolymers, methacrylate polymers, methacrylate copolymers, polyurethanes, polyvinylalcohol or a derivative thereof such as polyvinylacetate, silicone polymers and silicone copolymers, or copolymers thereof.

3. A composition according to claim 2, wherein the cellulose derivative is selected from the group consisting of ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose.

4. A composition according to claim 2, wherein the acrylic polymer is selected from the group consisting of methyl methacrylate and butyl methacrylate copolymer, ethyl acrylate and methyl methacrylate copolymer, acrylate and ammonium methacrylate copolymer type A and type B, and acrylates/octylacrylamide copolymer.

5. A composition according to any one of claims 1-4, wherein the plasticizer is selected from the group consisting of triethyl citrate, tributyl citrate, acetyl triethyl citrate, triacetin, dibutyl sebacate and polyethylene glycol 100-1000.

6. A composition according to any one of claims 1-5, wherein the oily release-enhancing agent is selected from the group consisting of

(a) a polyoxypropylene fatty alkyl ether;
(b) an isopropyl ester of a straight or branched chain C_{10-18} alkanoic or alkenoic acid;
(c) a propylene glycol mono- or diester of a C_{8-14} fatty acid;
(d) a straight or branched C_{8-24} alkanol or alkenol;
(e) a C_{6-22} acylglyceride;
(f) N-alkylpyrrolidone or N-alkylpiperidone; and

(g) a mineral oil such as liquid paraffin.

7. A composition according to claim 6, wherein the polyoxypropylene fatty alkyl ether is selected from the group consisting of polyoxypropylene-15-stearyl ether, polyoxypropylene-11-stearyl ether, polyoxypropylene-14-butyl ether, polyoxypropylene-10-cetyl ether or polyoxypropylene-3-myristyl ether.

8. A composition according to claim 6, wherein the isopropyl ester of a straight or branched chain C_{10-18} alkanoic or alkenoic acid is isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate or isopropyl monooleate.

9. A composition according to claim 6, wherein the propylene glycol monoester of a C_{8-14} fatty acid is propylene glycol monolaurate or propylene glycol monocaprylate, and wherein the propylene glycol diester of a C_{8-14} alkanoic acid is propylene glycol dipelargonate.

10. A composition according to claim 6, wherein the straight C_{8-24} alkanol is capryl, lauryl, cetyl, stearyl, oleyl, linoelyl or myristyl alcohol, or wherein the branched C_{8-24} alkanol is a branched C_{18-24} alkanol such as 2-octyldodecanol.

11. A composition according to claim 6, wherein the C_{6-22} acylglyceride is a vegetable oil, e.g. sesame oil, sunflower oil, palm kernel oil, corn oil, safflower oil, olive oil, avocado oil, jojoba oil, grape kernel oil, canola oil, wheat germ oil, almond oil, cottonseed oil, peanut oil, walnut oil or soybean oil, a highly purified vegetable oil, e.g. medium chain triglycerides (caprylic/capric triglycerides), long chain triglycerides, castor oil, caprylic monoglyceride, caprylic/capric mono- and diglycerides or caprylic/capric mono-, di- and triglycerides.

12. A composition according to claim 6, wherein the N-alkylpyrrolidone is N-methylpyrrolidone.

13. A composition according to any one of claims 1-12, wherein the propellant is dimethyl ether.

14. A composition according to any one of claims 1-13, wherein the second propellant a C_{3-5}alkane, preferably selected from the group consisting of n-propane, isopropane, n-butane or isobutane.

15. A composition according to claim 14, wherein the C_{3-5}alkane is n-butane and/or isobutane.

16. A composition according to claim 15, wherein the ratio of n-butane and/or isobutane to dimethyl ether is in the range of 6:1-0:1 v/v, such as 5:1-1:2, 4:1-1:1, 4:2-1:1, 4:2-4:3 or 4:2-1:1.

17. A composition according to any one of claims 1-16 which is essentially free from a low-molecular volatile solvent.

18. A composition according to any one of claims 1-17 which is substantially anhydrous.

19. A composition according to any one of claims 1-18 further comprising an anti-nucleating agent.

20. A composition according to claim 19, wherein the anti-nucleating agent is selected from the group consisting of polyvinyl alcohol, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, polyvinylpyrrolidone and carboxymethyl cellulose.

21. A composition according to any one of claims 1-20, wherein the therapeutically active ingredient is selected from the group consisting of vitamin D derivatives or analogues, corticosteroids, phosphodiesterase 4 inhibitors, ingenol derivatives, retinoids such as adapalene, JAK inhibitors, NK-1 receptor antagonists, calcineurin inhibitors such as tacrolimus or pimecrolimus, keratolytic agents such as salicylic acid or lactic acid, antibiotics such as fusidic acid or clindamycin, non-steroidal antiinflammatory agents and local anesthetics such as lidocain.

22. A composition according to claim 21 comprising calcipotriol or calcipotriol monohydrate as the vitamin D analogue and betamethasone dipropionate or valerate as the corticosteroid.

23. A pressurized container adapted to dispensing a topical composition on an affected skin area, the container including a container body comprising a composition according to any one of claims 1-22 and a valve assembly including an actuator for releasing the composition as a spray.

24. A container according to claim 23, wherein the valve assembly contains at least one aperture with a diameter of 0.05-1 mm.

25. A container according to claim 23, wherein the actuator is provided with an orifice with a diameter of 0.3-1.5 mm.

26. A composition according to any of claims 1-22 for use in the treatment of dermatological diseases or conditions.

27. A composition according to claim 26, wherein the dermatological disease or condition is selected from the group consisting of psoriasis, pustulosis palmoplantaris, ichtyosis, atopic dermatitis, contact dermatitis, eczema, actinic keratosis, pruritus, rosacea and acne.

Fig. 1

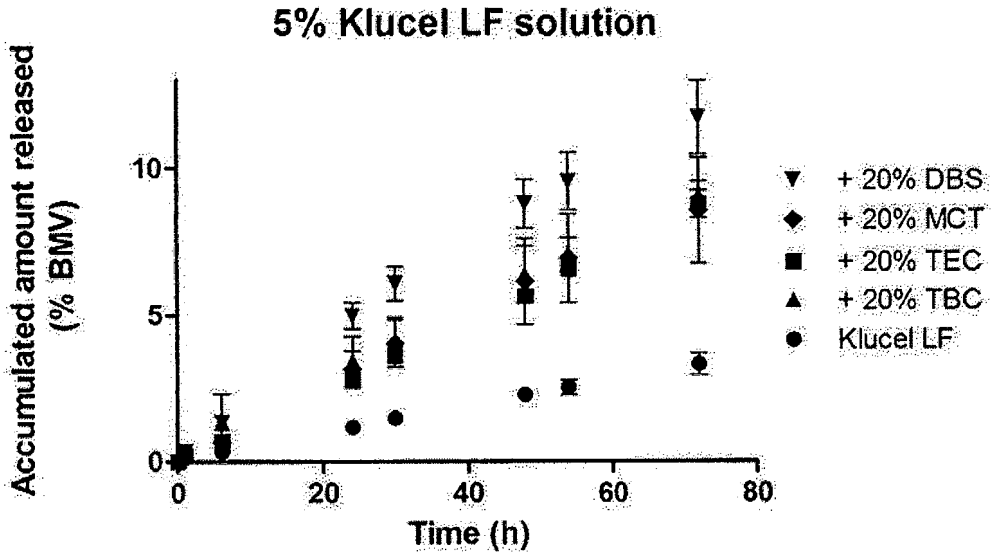

5% Klucel LF solution
Accumulated amount released (% BMV)
Time (h)
+ 20% DBS
+ 20% MCT
+ 20% TEC
+ 20% TBC
Klucel LF

Fig. 2

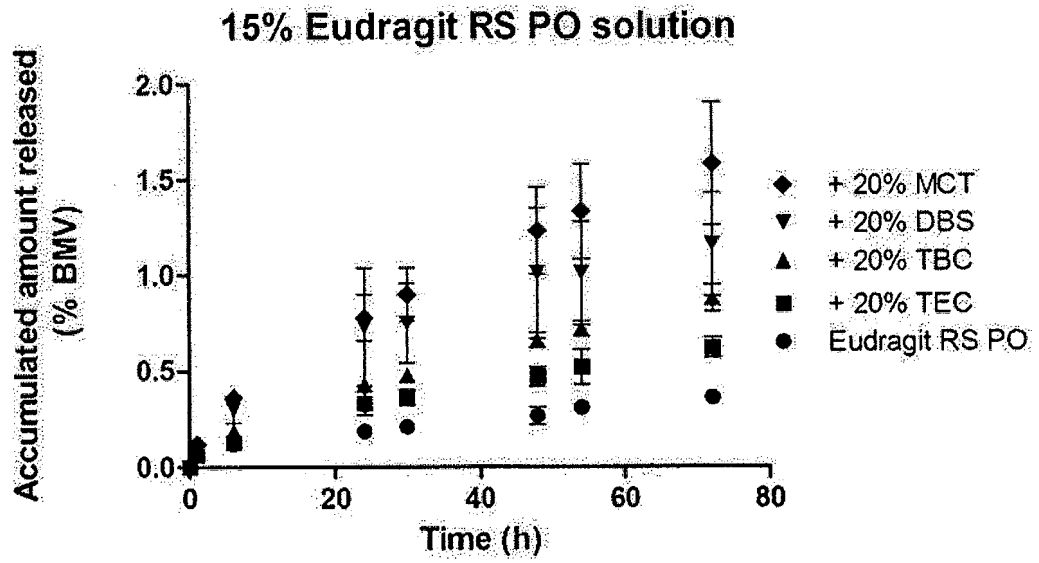

15% Eudragit RS PO solution
Accumulated amount released (% BMV)
Time (h)
+ 20% MCT
+ 20% DBS
+ 20% TBC
+ 20% TEC
Eudragit RS PO

Fig. 3

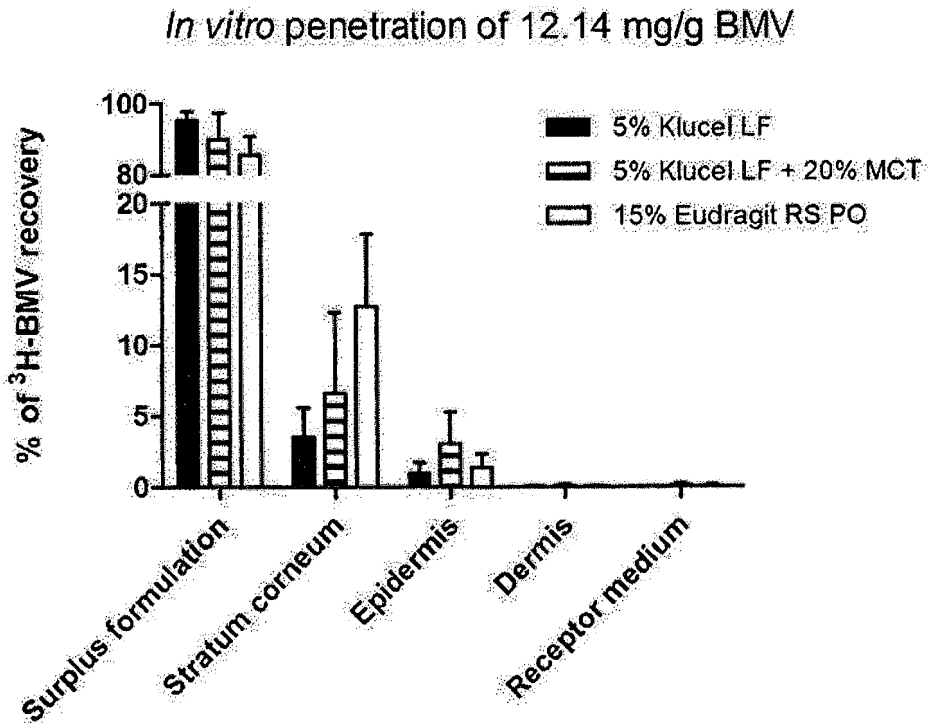

In vitro penetration of 12.14 mg/g BMV
% of ^{3}H-BMV recovery
100
80
20
15
10
5
0
5% Klucel LF
5% Klucel LF + 20% MCT
15% Eudragit RS PO
Surplus formulation
Stratum corneum
Epidermis
Dermis
Receptor medium

Fig. 4

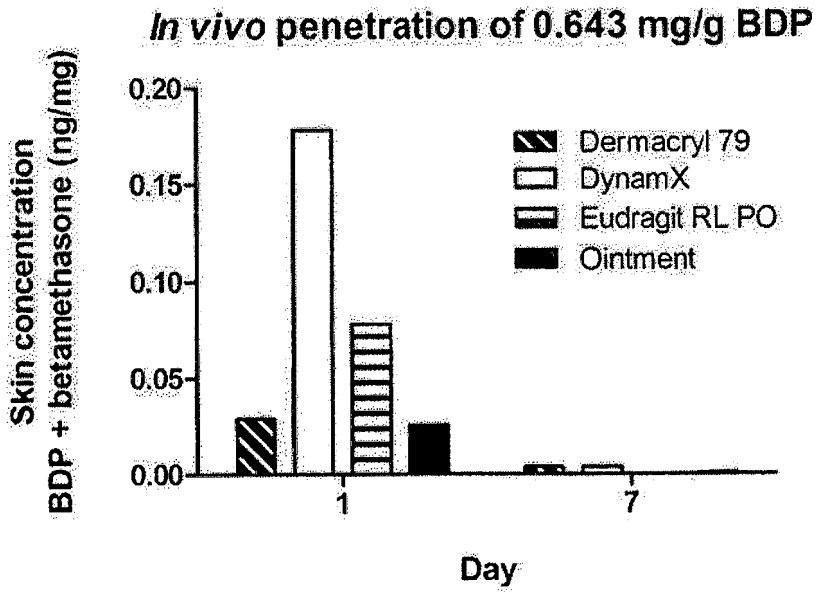
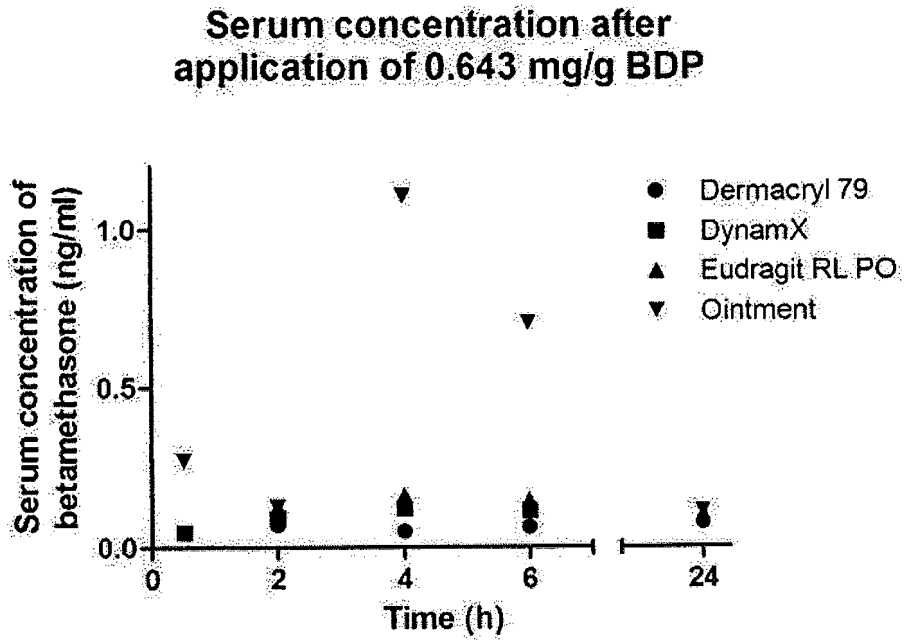

In vivo penetration of 0.643 mg/g BDP
Skin concentration
BDP + betamethasone (ng/mg)
0.20
0.15
0.10
0.05
0.00
1
7
Day
Dermacryl 79
DynamX
Eudragit RL PO
Ointment

Fig. 5


Serum concentration after application of 0.643 mg/g BDP
Serum concentration of betamethasone (ng/ml)
1.0
0.5
0.0
0
2
4
6
24
Time (h)
Dermacryl 79
DynamX
Eudragit RL PO
Ointment

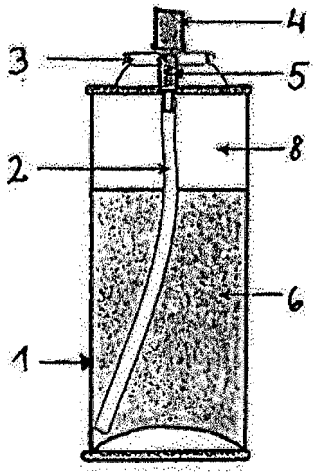


Fig. 6a

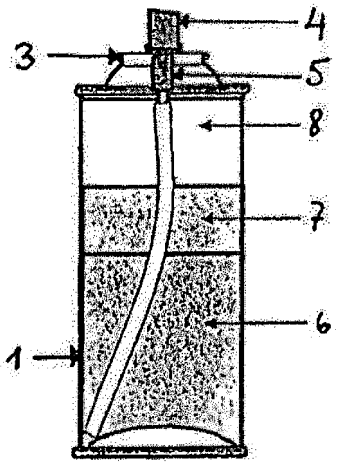


Fig. 6b

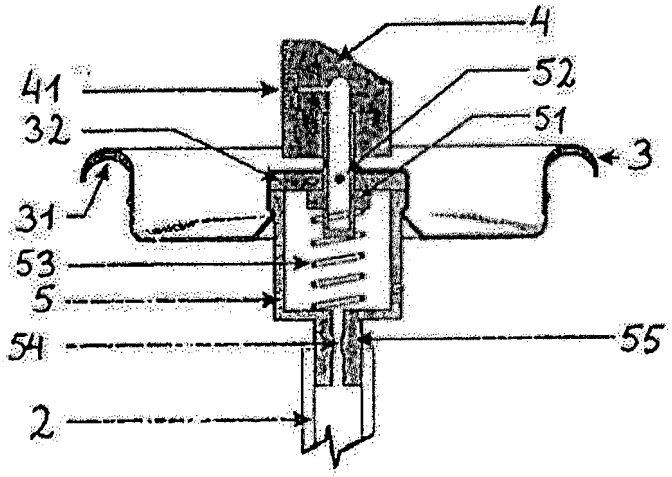


Fig. 7

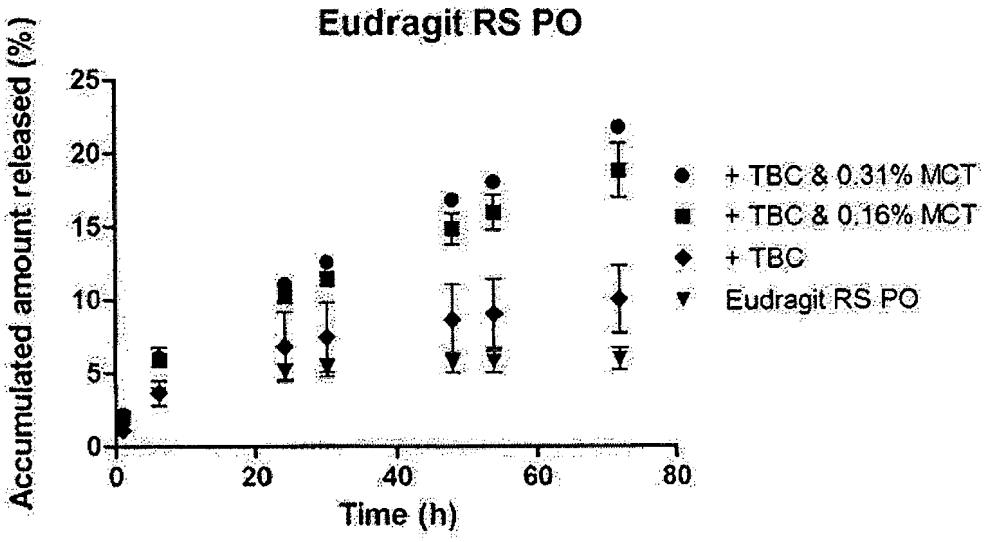

Eudragit RS PO
Accumulated amount released (%)
25
20
15
10
5
0
0
20
40
60
80
Time (h)
+ TBC & 0.31% MCT
+ TBC & 0.16% MCT
+ TBC
Eudragit RS PO

Fig. 8

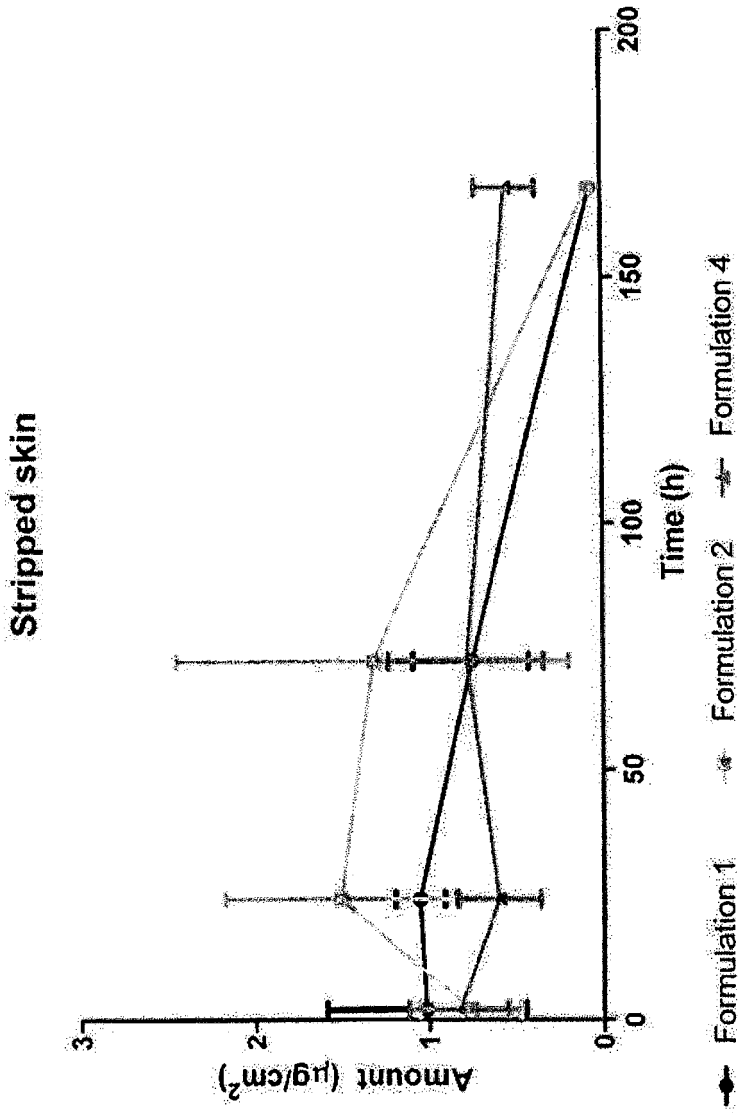

Stripped skin
Amount (µg/cm²)
0
1
2
3
0
50
100
150
200
Time (h)
Formulation 1
Formulation 2
Formulation 4

Fig. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064300

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/12 A61K9/70
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/45795 A2 (CIPLA LIMITED [IN]; WAIN CHRISTOPHER PAUL [GB]; LULLA AMAR [IN]; MALHO) 10 August 2000 (2000-08-10) page 2, paragraph 3 page 4, paragraph 4 page 5, paragraph 1 page 7, paragraph 3 - paragraph 5 page 6, paragraph 2 page 8, paragraphs 2,6 page 9, paragraphs 1,2 examples -----	1-27
Y	WO 2011/154004 A1 (LEO PHARMA AS [DK]; LIND MARIANNE [DK]; RASMUSSEN GRITT [DK]; SONNE ME) 15 December 2011 (2011-12-15) page 3, line 6 - line 11 page 4, line 11 - page 5, line 3 page 11, line 13 - line 23 -----	1-27

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2013	19/09/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dudás, Eszter

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/064300

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/213744 A1 (LULLA AMAR [IN] ET AL) 28 October 2004 (2004-10-28) page 1, paragraphs 0009,0010 page 2, paragraphs 0020,0021,0025 page 3, paragraphs 0030,0033,0038 -----	1-27
A	EP 0 521 455 A2 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]; OSAKA AEROSOL IND CORP [JP]) 7 January 1993 (1993-01-07) page 2, line 47 - line 52 page 3, line 30 - line 43 page 4, line 20 - line 35 -----	1-27

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/064300

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0045795 A2	10-08-2000	AT 252380 T	15-11-2003
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		DE 60006069 D1	27-11-2003
		DE 60006069 T2	29-07-2004
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EP 0521455 A2	07-01-1993	CA 2072812 A1	03-01-1993
		EP 0521455 A2	07-01-1993

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104519869 A
(43)申请公布日 2015.04.15

(21)申请号 201380040976.5
(22)申请日 2013.07.05
(30)优先权数据
61/668,846 2012.07.06 US
(85)PCT国际申请进入国家阶段日
2015.02.02
(86)PCT国际申请的申请数据
PCT/EP2013/064300 2013.07.05
(87)PCT国际申请的公布数据
WO2014/006201 EN 2014.01.09
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(51)Int.Cl.
A61K 9/00(2006.01)
A61K 9/12(2006.01)
A61K 9/70(2006.01)

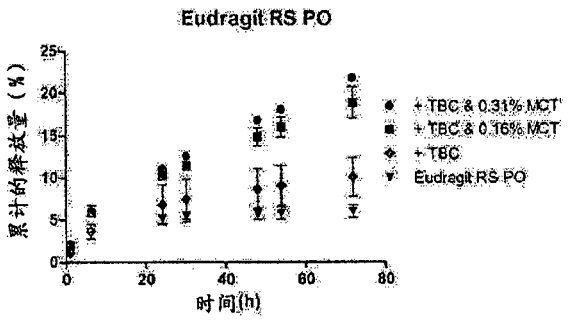
权利要求书2页 说明书17页 附图5页

(54)发明名称

用于递送活性成分至皮肤的包含成膜聚合物的局部组合物

(57)摘要

用于皮肤涂敷的可喷雾的成膜药物组合物，所述组合物包含至少一种溶解于药学上可接受的推进剂中的治疗活性成分，所述推进剂选自二甲醚、乙醚和甲乙醚，以及二甲醚、乙醚和甲乙醚与选自C_{3-5}烷烃、氢氟烷烃、氢氯烷烃、氟烷烃和氯氟烷烃的第二种推进剂的混合物，所述推进剂以50-99.5% w/w的组合物的量存在，所述组合物还包含成膜聚合物、增塑剂和油性释放增强剂。



CN 104519869 A

1. 用于皮肤涂敷的可喷雾的成膜药物组合物，所述组合物包含至少一种溶解于药学上可接受的推进剂中的治疗活性成分，所述推进剂选自二甲醚、乙醚和甲乙醚，以及二甲醚、乙醚和甲乙醚与选自 C_{3-5}烷烃、氢氟烷烃、氢氯烷烃、氟烷烃和氯氟烷烃的第二种推进剂的混合物，所述推进剂以 50-99.5% w/w 的组合物的量存在，所述组合物还包含 0.1-50% w/w 的量的成膜聚合物、0.1-10% w/w 的量的增塑剂和 0.1-15% w/w 的量的油性释放增强剂。

2. 根据权利要求 1 的组合物，其中所述成膜聚合物选自由纤维素衍生物、丙烯酸聚合物、丙烯酸共聚物、甲基丙烯酸酯聚合物、甲基丙烯酸酯共聚物、聚氨酯、聚乙烯醇或其衍生物例如聚乙酸乙烯酯、硅酮聚合物和硅酮共聚物、或其共聚物组成的组。

3. 根据权利要求 2 的组合物，其中所述纤维素衍生物选自由乙基纤维素、甲基纤维素、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素组成的组。

4. 根据权利要求 2 的组合物，其中所述丙烯酸聚合物选自由甲基丙烯酸甲酯和甲基丙烯酸丁酯共聚物、丙烯酸乙酯和甲基丙烯酸甲酯共聚物、丙烯酸酯和甲基丙烯酸铵共聚物 A 型和 B 型、以及丙烯酸酯 / 辛基丙烯酰胺共聚物组成的组。

5. 根据权利要求 1-4 中任一项的组合物，其中所述增塑剂选自由柠檬酸三乙酯、柠檬酸三丁酯、乙酰基柠檬酸三乙酯、三乙酸甘油酯、癸二酸二丁酯和聚乙二醇 100-1000 组成的组。

6. 根据权利要求 1-5 中任一项的组合物，其中所述油性释放增强剂选自由以下组成的组：

(a) 聚氧丙烯脂肪烷基醚；

(b) 直链或支链 C_{10-18}链烷酸或链烯酸的异丙酯；

(c) C_{8-14}脂肪酸的丙二醇单酯或二酯；

(d) 直链或支链 C_{8-24}烷醇或链烯醇；

(e) C_{6-22}酰基甘油酯；

(f) N- 烷基吡咯烷酮或 N- 烷基哌啶酮；和

(g) 矿物油，例如液体石蜡。

7. 根据权利要求 6 的组合物，其中所述聚氧丙烯脂肪烷基醚选自由聚氧丙烯 -15- 硬脂基醚、聚氧丙烯 -11- 硬脂基醚、聚氧丙烯 -14- 丁基醚、聚氧丙烯 -10- 鲸蜡基醚或聚氧丙烯 -3- 肉豆蔻基醚组成的组。

8. 根据权利要求 6 的组合物，其中所述直链或支链 C_{10-18}链烷酸或链烯酸的异丙酯为肉豆蔻酸异丙酯、棕榈酸异丙酯、异硬脂酸异丙酯、亚油酸异丙酯或单油酸异丙酯。

9. 根据权利要求 6 的组合物，其中所述 C_{8-14}脂肪酸的丙二醇单酯为丙二醇单月桂酸酯或丙二醇单辛酸酯，并且其中所述 C_{8-14}链烷酸的丙二醇二酯为二壬酸丙二醇酯。

10. 根据权利要求 6 的组合物，其中所述直链 C_{8-24}烷醇为辛醇、月桂醇、鲸蜡醇、硬脂醇、油醇、亚油醇或肉豆蔻醇，或其中所述支链 C_{8-24}烷醇为支链 C_{18-24}烷醇例如 2- 辛基十二烷醇。

11. 根据权利要求 6 的组合物，其中所述 C_{6-22}酰基甘油酯为植物油，例如芝麻油、向日葵油、棕榈仁油、玉米油、红花油、橄榄油、鳄梨油、希蒙得木油、葡萄籽油、菜籽油、麦胚油、杏仁油、棉籽油、花生油、核桃油或大豆油，高度纯化的植物油、例如中链甘油三酯（辛酸 / 癸酸甘油三酯）、长链甘油三酯、蓖麻油、辛酸甘油单酯、辛酸 / 癸酸甘油单酯和甘油二酯或

辛酸 / 癸酸甘油单酯、甘油二酯和甘油三酯。

12. 根据权利要求 6 的组合物，其中所述 N- 烷基吡咯烷酮为 N- 甲基吡咯烷酮。

13. 如权利要求 1-12 中任一项的组合物，其中所述推进剂是二甲醚。

14. 如权利要求 1-13 中任一项的组合物，其中第二种推进剂是 C_{3-5} 烷烃，优选地选自正丙烷、异丙烷、正丁烷或异丁烷。

15. 如权利要求 14 中所述的组合物，其中所述 C_{3-5} 烷烃是正丁烷和 / 或异丁烷。

16. 如权利要求 15 中所述的组合物，其中正丁烷和 / 或异丁烷与二甲醚的比例是在 6:1-0:1v/v 的范围，例如 5:1-1:2、4:1-1:1、4:2-1:1、4:2-4:3 或 4:2-1:1。

17. 如权利要求 1-16 中任一项的组合物，其基本上不含低分子挥发性溶剂。

18. 如权利要求 1-17 中任一项的组合物，其为基本上无水的。

19. 如权利要求 1-18 中任一项的组合物，其进一步包含抗成核剂。

20. 根据权利要求 19 的组合物，其中所述抗成核剂选自由聚乙烯醇、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素、聚乙烯吡咯烷酮和羧甲基纤维素组成的组。

21. 根据权利要求 1-20 中任一项的组合物，其中所述治疗活性成分选自由以下组成的组 ：维生素 D 衍生物或类似物、皮质类固醇、磷酸二酯酶 4 抑制剂、巨大戟醇衍生物、类视黄醇类例如阿达帕林、JAK 抑制剂、NK-1 受体拮抗剂、钙调磷酸酶抑制剂例如他克莫司或吡美莫司、溶角蛋白剂例如水杨酸或乳酸、抗生素例如夫西地酸或克林霉素、非甾体抗炎剂和局部麻醉剂例如利多卡因。

22. 根据权利要求 21 的组合物，其包含卡泊三醇或卡泊三醇一水合物作为所述维生素 D 类似物以及二丙酸倍他米松或戊酸倍他米松作为所述皮质类固醇。

23. 适合在患病皮肤区域分配局部组合物的加压容器，该容器包括 ：含有如权利要求 1-22 中任一项所述的组合物的容器本体以及包含用于释放以喷雾形式的组合物的致动器的阀组件。

24. 如权利要求 23 中所述的容器，其中阀组件包含至少一个 0.05-1mm 直径的开孔。

25. 如权利要求 23 中所述的容器，其中致动器具有 0.3-1.5mm 直径的孔口。

26. 根据权利要求 1-22 中任一项的组合物，其用于治疗皮肤疾病或疾患。

27. 根据权利要求 26 的组合物，其中所述皮肤疾病或疾患选自由银屑病、掌跖脓疱病、鱼鳞病、特应性皮炎、接触性皮炎、湿疹、光化性角化病、瘙痒症、酒糟鼻和痤疮组成的组。

用于递送活性成分至皮肤的包含成膜聚合物的局部组合物

发明领域

[0001] 本发明涉及用于涂敷于皮肤上并且含有成膜聚合物和至少一种活性成分的可喷雾的药物组合物，所述组合物在推进剂蒸发时在皮肤上形成薄的透明膜。

[0002] 发明背景

[0003] 人的皮肤，特别是外层、角质层，提供了抵抗微生物病原体和毒性化学物质穿透的有效屏障。尽管这种皮肤性质通常有益，但是其使药物的皮肤施用复杂化，因为涂敷于罹患皮肤疾病的患者的皮肤上的大量（如果不是大多数）活性成分可能未穿透进入到发挥其活性的有活力的皮肤层。为了确保活性成分充分穿透到皮肤和表皮中，一般优选包括呈溶解状态的活性成分，通常在还可用作活性成分的穿透增强剂的低分子挥发性溶剂诸如醇，例如乙醇或二醇（例如丙二醇）存在下。使活性成分穿透进入皮肤的另一种方法是通过在疏水性媒介物诸如矿脂中配制活性成分来提供包藏。然而，含有矿脂的软膏剂一般具有在涂敷后持续很长一段时间的发粘感或滑腻感，并因此在美容学上是不可接受的。

[0004] 作为常规制剂诸如软膏剂的替代方案，已开发含有已掺入活性成分的成膜聚合物的组合物。成膜组合物主要用于提供活性成分的经皮递送，诸如在经皮贴剂中，或者最近作为由成膜聚合物、增塑剂和用于活性成分的低分子挥发性溶剂组成的成膜溶液。当所述溶液涂敷于皮肤上时，在蒸发溶剂后形成薄的聚合物膜。

[0005] EP 515 312 B1 公开了含有作为活性成分的特比萘芬和成膜聚合物例如聚乙酸乙烯酯或丙烯酸酯和甲基丙烯酸酯共聚物的局部用制剂，其在治疗甲癣中用作指甲油。

[0006] WO 2006/111426 公开了在治疗指甲银屑病中用作指甲油的含有维生素 D 衍生物和皮质类固醇的成膜溶液。成膜聚合物可选自聚乙烯吡咯烷酮、聚乙烯基甲基醚的丁酯和马来酸共聚物以及丙烯酸酯和甲基丙烯酸铵共聚物。组合物可含有作为溶剂的乙醇并且可另外含有穿透增强剂。

[0007] US 2007/0248658 公开了包含成膜的聚氨酯或聚氨酯和丙烯酸酯共聚物以及一种或多种活性成分的组合物，用于皮肤或经皮递送一种或多种活性成分诸如炔雌醇。组合物可另外含有低分子挥发性溶剂诸如乙醇或异丙醇以及穿透增强剂诸如油酸、油醇、丙二醇、碳酸丙烯酯、N- 甲基吡咯烷酮和肉豆蔻酸异丙酯。

[0008] US 2004/0213744 公开了用于局部涂敷的可喷涂组合物，包含成膜聚合物、渗透增强剂、增溶剂、增塑剂和活性成分。成膜聚合物可以为丙烯酸聚合物或共聚物、甲基丙烯酸聚合物或共聚物、聚乙酸乙烯酯、聚乙烯醇、聚乙烯吡咯烷酮或纤维素聚合物。渗透增强剂可选自表面活性剂、油酸、癸酸和辛酸的混合物酯、多元醇、肉豆蔻酸异丙酯等。增溶剂可以为表面活性剂、多元醇或二甲胺乙基甲基丙烯酸酯的共聚物和甲基丙烯酸酯共聚物。增塑剂可选自柠檬酸三乙酯、异山梨醇二甲醚、乙酰基柠檬酸三丁酯、蓖麻油、丙二醇等。组合物还可以包括推进剂，例如烃、氢氟烃、二甲醚、氮、二氧化碳等。

[0009] WO 2007/031753 公开了成膜组合物，其包含以至少 80％饱和度存在的活性成分、成膜聚合物诸如聚乙烯吡咯烷酮、聚乙烯醇、丙烯酸聚合物及共聚物、甲基丙烯酸聚合物及共聚物和纤维素聚合物、低分子挥发性溶剂诸如乙醇、推进剂诸如氢氟烷烃，以及优选还包

含抗成核剂诸如聚乙烯醇和增塑剂诸如甘油、聚乙二醇、油酸、柠檬酸、脂肪酸酯、烃等。

[0010] 本发明的目的是提供薄且透明的成膜组合物，以使它们在皮肤上形成近乎看不见的膜，所述膜为柔性的、快速干燥的且非粘性的。

[0011] 本发明的另一目的是提供能够在延长的时段内将掺入其中的活性成分释放到皮肤上层的成膜组合物，以使组合物的施用频率低于常规局部组合物例如霜剂、软膏剂或凝胶。

[0012] 本发明的另一个目的是在不包含常规透皮促进剂（例如醇类或丙二醇，其为有效的皮肤刺激剂）情况下提供具有改善掺入其中的活性成分向皮肤上层（尤其是角质层）的穿透的成膜组合物。在此情况下，角质层可以充当贮库，从其中逐渐释放活性成分。

[0013] 本发明的又一目的是提供其中活性成分在组合物的整个贮存期限中未被显著降解，而保持在化学和物理上稳定的组合物。

[0014] 发明概述

[0015] 在文献中公开的成膜组合物具有掺入其中的活性成分仅较小比例从组合物释放的缺点。在导致本发明的研究中，我们已令人惊讶地发现，如果将油性组分加入到成膜组合物，可增加活性成分随着时间从所得膜中的释放。因此，可能在数天的时间内获得活性成分的缓释并因此省去每天涂敷局部组合物（这目前是标准操作）。此外，其可能提供在该组合物中不包含常规透皮促进剂的情况下活性成分向皮肤内的充分穿透性。

[0016] 因此，一方面，本发明涉及用于皮肤施用的可喷雾的成膜药物组合物，所述组合物包含至少一种溶解于药学上可接受的推进剂（选自二甲醚、乙醚和甲乙醚，以及二甲醚、乙醚和甲乙醚和选自 C_{3-5}烷烃、氢氟烷烃、氢氯烷烃、氟烷烃和氯氟烷烃的第二种推进剂的混合物）中的治疗活性成分，所述推进剂以 50-99.5% w/w 的组合物的量存在，所述组合物还包含 0.1-50% w/w 的量的成膜聚合物、0.1-10% w/w 的量的增塑剂和 0.1-15% w/w 的量的油性释放增强剂。

[0017] 已发现本发明的成膜组合物在涂敷于皮肤上时形成薄的透明膜。所述组合物几乎看不见，因此与可见的贴剂相比在美容学上更为患者所接受。成膜组合物快速干燥且为非粘性，因此避免粘结于患者的衣服。当测试亲合性 (substantivity)，即在涂敷于皮肤上后抵抗由洗涤或普通穿着所产生的磨损的能力时，包含疏水性成膜聚合物的组合物相对于含有亲水性成膜聚合物的组合物趋于展现出在皮肤上的亲合性增加。此外，油性的释放增强剂可用作润肤剂以改善皮肤的水化以及控制经表皮的水损失，因此增强成膜聚合物的封闭效果。

[0018] 在另一方面，本发明涉及本文公开的用于治疗皮肤疾病和疾患的组合物。

[0019] 本发明的组合物可以从气雾剂容器中进行分配，通常该类型包含容器本体和阀组件。该容器本体可以例如包含金属本体，其优选地用化学惰性的涂覆物质涂覆内衬，以避免因容器本体与组合物之间相互作用引起的组合物降解。

[0020] 阀组件可以包含阀座（有时指安装座 (mounting cup)）、带有阀杆的阀体或壳体、弹簧、浸管和致动器。内部垫圈通常密封阀杆中的孔洞，但当操作致动器时，阀杆移动，使得所述孔洞打开。一旦打开，由容器本体内推进剂产生的压力促使组合物经该孔洞流入浸管和阀杆中，并经致动器流出。应当理解，当致动器松开时，阀弹簧将阀杆恢复原位，使得所述孔洞再次密封。

[0021] 所述阀杆和致动器各自包含一个或多个孔洞（孔口）和通道，其数量、大小和形状由所连接的具体组合物制剂的物理性质所决定，从而控制经过阀的流速以及从致动器中出现的喷雾的特性。

[0022] 喷雾样式和流速可以通过装入致动器出口孔的独立的插入物来控制，其提供了致动器组件的终端孔口。通往出口的经该插入物的通道通常包含直径比致动器主体中的通道狭窄的部分，使得进入插入物通道中的从致动器通道中出现的流体被引起漩涡并打碎成微滴。所述插入物可具有一定轮廓（例如其可以是阶梯状），使得所述组合物被迫向前并向前运动而非更加平常的旋转运动流出终端孔口。这获得了均匀的或连续的（solid）喷雾形式，并因此使得使用者较好地将该组合物集中在需要治疗的皮肤区域。

[0023] 由于不期望本发明的组合物被吸入，优选地选择所述流体通道、孔口、插入物等的尺寸以避免在排驱作用下产生细雾。

[0024] 阀组件可以包含计量阀，使得致动器每次启动时仅分配计量的量的组合物。

[0025] 出于存储、安全性和／或卫生原因，可提供带有保护套或封盖的致动器，其与致动器分离或作为整体。该封盖可以从第一个位置（此时终端孔口密封）移至第二个位置（此时所述孔口打开）；在第二个位置，该封盖还可以用作定向喷嘴以限制喷洒区域。该致动器自身可以包含一个简单的按钮致动器，或可以例如包含拉盖或旋锁。在另一种情况下，带有整体手指致动器的封盖可以确保容器的安全，并覆盖位于下面的致动器按钮。该封盖的底面可以包含例如多个突出物，用于一旦由于手指按压操作器而发生移动就接触致动器按钮，并触发阀打开。

[0026] 或者，或除此以外，致动器可以在阻止阀被有意或无意操作的第一个位置与第二个可操作的位置之间移动。例如，部分阀组件可以是阀杆可旋转的，例如在一个旋转位置上该致动器可操作分配产品，而在另一个旋转位置上该致动器与容器上的突出物或接合点对准以阻止启动。这类“旋转并喷雾”的机械装置可以包含开启和关闭位置的触觉或听觉指示。

[0027] 需要包含防篡改封签，其在气雾剂容器首次使用前必须被破坏。

附图说明

[0028] 图 1 显示，与戊酸倍他米松（BMV）从不含增塑剂或油性释放增强剂的成膜组合物的释放相比，在 72 小时的时间内 BMV 从含有 Klucel LF 和 20％（以干燥的成膜聚合物的重量计）的增塑剂 TEC、TBC 和 DBS、或油性释放增强剂 MCT 的成膜组合物的释放。

[0029] 图 2 显示，与 BMV 从不含增塑剂或油性释放增强剂的成膜组合物的释放相比，在 72 小时的时间内 BMV 从含有 Eudragit RS PO 和 20％（以干燥的成膜聚合物的重量计）的增塑剂 TEC、TBC 和 DBS、或油性释放增强剂 MCT 的成膜组合物的释放。

[0030] 图 3 显示在 24 小时的过程中来自所有三种测试组合物的 BMV 的穿透。

[0031] 图 4 显示在 1 天和 7 天后在无毛大鼠皮肤中二丙酸倍他米松（BDP）及其代谢物倍他米松的浓度。

[0032] 图 5 显示将成膜组合物和对比的软膏剂涂敷于无毛大鼠皮肤上在 24h 内倍他米松的血清浓度。

[0033] 图 6a 显示用于受压喷洒本发明组合物的容器的横截面，包括容器本体（1），其上

装有包含阀座 (3)、阀体 (5)、致动器 (4) 和浸管 (2) 的阀组件。如该实施方案中所示，组合物可以是包含组合物相 (6) 和气相 (8) 的两相系统。

[0034] 图 6b 显示用于受压喷洒本发明组合物的容器的横截面，包括容器本体 (1)，其上装有包含阀座 (3)、阀体 (5)、致动器 (4) 和浸管 (2) 的阀组件。如该实施方案中所示，组合物可以是包含媒介物相 (6)、推进剂相 (7) 和气相 (8) 的三相系统。

[0035] 图 7 显示装在容器本体 (1) 的本体上的阀组件的横截面，包括：阀座 (3)，其具有容器本体 (1) 和阀座 (3) 之间的封口 (31) 和垫圈 (32)；阀体 (5)，其具有与致动器 (4) 连接的阀杆 (51) 和弹簧 (53)，所述致动器具有带有末端孔口 (41) 的插入物 (44)，当按压致动器 (4) 时存在于容器本体 (1) 中的组合物通过孔口被排出。阀杆 (51) 包含一个开孔 (52)，当按压致动器时存在于容器本体 (1) 中的组合物可通过其流出。阀体还具有尾管 (tailpiece)(55)，浸管 (2) 与尾管连接。尾管 (55) 具有一个开孔 (54)，使得组合物可以从浸管 (2) 中流出。

[0036] 图 8 是显示成膜组合物的累积的 BDP 释放量作为时间的函数的图，所述成膜组合物只包含作为成膜聚合物的 Eudragit RS PO、包含 Eudragit RS PO 与作为增塑剂的柠檬酸三丁酯、或者包含 Eudragit RS PO 与柠檬酸三丁酯和作为油性释放增强剂的 0.16% w/w 或 0.31% w/w MCT。

[0037] 图 9 是显示施用包含单独的 Eudragit RS PO(制剂 1)、Eudragit RS PO 和柠檬酸三丁酯 (制剂 2)、Eudragit RS PO、柠檬酸三丁酯和 0.16% w/w MCT(制剂 4) 后，无毛豚鼠皮肤中活性成分 (BDP) 的量作为时间的函数的图。

[0038] 发明详述

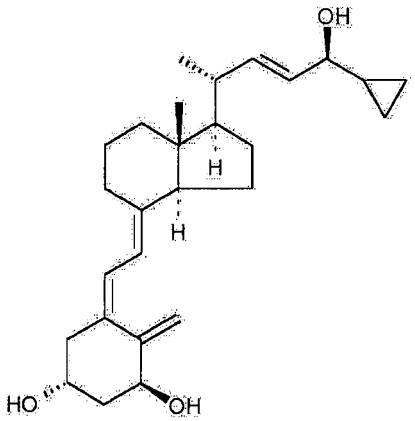
[0039] 定义

[0040] 术语“维生素 D 衍生物”旨在指示维生素 D_3 的生物活性代谢物，诸如骨化三醇、或此类代谢物的前体，诸如阿法骨化醇。

[0041] 术语“维生素 D 类似物”旨在指示采用侧链修饰和 / 或骨架自身修饰的包含维生素 D 骨架的合成化合物。类似物展现出对维生素 D 受体具有与天然存在的维生素 D 化合物类似的生物活性。

[0042] “卡泊三醇”是具有下式的维生素 D 类似物，

[0043]



[0044] 已发现卡泊三醇以两种结晶形式存在：无水物和一水合物。卡泊三醇一水合物及其制备公开于 WO 94/15912 中。

[0045] 术语“储存稳定性”或“储存稳定的”旨在表示所述组合物展现出化学和物理稳定性，其特征在于允许所述组合物在冷冻或优选在室温下储存足够长的时间段，以使所述组合物是商业上可用的，诸如储存至少 12 个月，特别地是至少 18 个月，优选至少 2 年。

[0046] 术语“化学稳定性”或“化学稳定的”旨在表示在室温下，在产品的贮存期限内（通常 2 年）不多于 10%、优选不多于 6% 的活性成分降解。通过使所述组合物在 40℃ 进行加速的稳定性研究可获得在室温下的化学稳定性的近似值，在所述稳定性研究中将所述组合物置于 40℃ 的加热橱柜并且于 1、2 和 3 个月采集样品并通过 HPLC 测试降解产物的存在。如果少于约 10% 的物质在 40℃ 的 3 个月后降解，则这通常对应于在室温下 2 年的贮存期限。当包括于所述组合物中的活性成分为卡泊三醇时，“化学稳定性”通常指示在药物成品中卡泊三醇随着时间推移未显著降解成 24- 表卡泊三醇或卡泊三醇的其它降解产物。

[0047] 术语“物理稳定性”或“物理稳定的”旨在表示在所述组合物的整个贮存期限中，活性成分未从推进剂或媒介物相沉淀。

[0048] 术语“基本上无水”旨在表示软膏剂组合物中的游离水含量不超过所述组合物重量的约 2%，优选不超过约 1%。

[0049] 术语“中链甘油三酯”用于表示具有 6-12 个碳原子链长的脂肪酸的甘油三酯。此类中链甘油三酯目前的优选实例是辛酸 (C_8) 和癸酸 (C_{10}) 甘油三酯的混合物，例如可以商品名 Miglyol 812 获得。

[0050] 术语“皮肤穿透 (penetration)”旨在表示活性成分扩散进入皮肤的不同层，即角质层、表皮和真皮。

[0051] 术语“皮肤渗透 (permeation)”旨在表示活性成分穿过皮肤进入全身循环的流动，或进入用于实验中的 Franz 细胞装置的接受室的流体。

[0052] 术语“释放”旨在指示当其涂敷于表面例如硅酮膜上时离开所述组合物的活性成分的量。穿过该膜的体外释放可以通过实施例 2 中公开的方法确定。在该上下文中，术语“缓释”旨在表示在至少 48 小时诸如 72 小时的时间内发生的活性成分的释放。术语“增加的释放”旨在指示与含有单独的成膜聚合物或含有成膜聚合物和增塑剂但不含油性释放增强剂的成膜组合物相比，随着时间推移从含有增塑剂和油性释放增强剂两者的成膜组合物中释放的活性成分的总量增加。

[0053] 使用术语“低分子挥发性溶剂”是指低级醇，例如甲醇、乙醇、异丙醇或丁醇；C_{1-4} 羧酸的 C_{1-4} 酯，例如乙酸甲酯、乙酸乙酯、乙酸丁酯、甲酸甲酯或丙酸丙酯；或者丙酮。

[0054] 实施方案

[0055] 在本发明的组合物中，成膜聚合物可选自由纤维素衍生物、丙烯酸聚合物、丙烯酸共聚物、甲基丙烯酸酯聚合物、甲基丙烯酸酯共聚物、聚氨酯、聚乙烯醇或其衍生物诸如聚乙酸乙烯酯、硅酮聚合物和硅酮共聚物、或其共聚物组成的组。

[0056] 当成膜聚合物为纤维素衍生物时，其可选自由乙基纤维素、甲基纤维素、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素组成的组。

[0057] 当成膜聚合物为丙烯酸聚合物时，其可选自由甲基丙烯酸甲酯和甲基丙烯酸丁酯共聚物、丙烯酸乙酯和甲基丙烯酸甲酯共聚物、丙烯酸酯和甲基丙烯酸铵共聚物 A 型和 B 型、以及丙烯酸酯 / 辛基丙烯酰胺共聚物组成的组。

[0058] 在本发明的组合物中，增塑剂可选自由柠檬酸三乙酯、柠檬酸三丁酯、乙酰基柠檬

酸三乙酯、三乙酸甘油酯、癸二酸二丁酯和聚乙二醇 100-1000 例如聚乙二醇 400 组成的组。

[0059] 将增塑剂掺入成膜组合物可使成膜聚合物的玻璃化转变温度 (Tg) 降低。当聚合膜在低于 Tg 的温度下为柔性时，Tg 是膜柔韧性的间接指标。因此，低于皮肤温度的 Tg 值指示该膜在皮肤上为柔性的。在具体实施方案中，对于含有丙烯酸聚合物作为成膜聚合物和柠檬酸三乙酯作为增塑剂的成膜组合物而言，已经获得了降低的 Tg。

[0060] 油性释放增强剂可选自由以下组成的组：

[0061] (a) 聚氧丙烯脂肪烷基醚；

[0062] (b) 直链或支链 C_{10-18}链烷酸或链烯酸的异丙酯；

[0063] (c) C_{8-14}脂肪酸的丙二醇单酯或二酯；

[0064] (d) 直链或支链 C_{8-24}烷醇或链烯醇；

[0065] (e) C_{6-22}酰基甘油酯；

[0066] (f) N- 烷基吡咯烷酮或 N- 烷基哌啶酮；和

[0067] (g) 矿物油，诸如液体石蜡。

[0068] 当油性释放增强剂为聚氧丙烯脂肪烷基醚时，其可选自由聚氧丙烯 -15- 硬脂基醚、聚氧丙烯 -11- 硬脂基醚、聚氧丙烯 -14- 丁基醚、聚氧丙烯 -10- 鲸蜡基醚或聚氧丙烯 -3- 肉豆蔻基醚组成的组。

[0069] 当油性释放增强剂为直链或支链 C_{10-18}链烷酸或链烯酸的异丙酯时，其可选自由肉豆蔻酸异丙酯、棕榈酸异丙酯、异硬脂酸异丙酯、亚油酸异丙酯或单油酸异丙酯组成的组。

[0070] 当油性释放增强剂为 C_{8-14}脂肪酸的丙二醇单酯时，其可以为丙二醇单月桂酸酯或丙二醇单辛酸酯，并且当其为 C_{8-14}链烷酸的丙二醇二酯时，其可以为二壬酸丙二醇酯。

[0071] 当油性释放增强剂为直链 C_{8-24}烷醇时，其可以为辛醇、月桂醇、鲸蜡醇、硬脂醇、油醇、亚油醇或肉豆蔻醇，或当其为支链 C_{8-24}烷醇时，其可以为支链 C_{18-24}烷醇如 2- 辛基十二烷醇。

[0072] 当油性释放增强剂为 C_{6-22}酰基甘油酯时，其可以为植物油，例如芝麻油、向日葵油、棕榈仁油、玉米油、红花油、橄榄油、鳄梨油、希蒙得木油 (jojoba oil)、葡萄籽油、菜籽油、麦胚油、杏仁油、棉籽油、花生油、核桃油或大豆油、高度纯化的植物油，例如中链甘油三酯 (辛酸 / 癸酸甘油三酯)、长链甘油三酯、蓖麻油、辛酸甘油单酯、辛酸 / 癸酸甘油单酯和甘油二酯或辛酸 / 癸酸甘油单酯、甘油二酯和甘油三酯。

[0073] 已经发现，使用纯的 C_{3-5}烷烃 (例如丁烷) 作为推进剂不能促成活性成分的有效溶解，因此活性成分可能随时间从溶液中沉淀出来，并导致晶体生长，因此该组合物在整个贮存期内物理上不稳定。此外，已经发现当独立使用二甲醚作为推进剂时或者甚至将一定比例的二甲醚加入 C_{3-5}烷烃中形成推进剂混合物时，该问题可以减到最低。因此，目前优选的实施方案中，组合物包含二甲醚作为单独推进剂或者与作为第二种推进剂的 C_{3-5}烷烃混合。

[0074] 在组合物中，C_{3-5}烷烃优选地选自正丙烷、异丙烷、正丁烷或异丁烷。特别优选的 C_{3-5}烷烃是正丁烷和 / 或异丁烷。

[0075] 在推进剂混合物中，正丁烷和 / 或异丁烷与二甲醚的比例可以优选地是在 6:1-0:1v/v 的范围，例如 5:1-1:2、4:1-1:1、4:2-1:1、4:2-4:3 或 4:3-1:1。

[0076] 如果需要，本组合物可以包含共溶剂，其是低分子挥发性溶剂。但是，目前优选地，由于在皮肤上应用时该溶剂的潜在刺激作用，本组合物基本上不含低分子挥发性溶剂。

[0077] 该组合物可以包含少量的水（其用作另外的增塑剂或共溶剂）。然而，目前优选所述组合物为基本上无水的。

[0078] 为了减少或延迟活性成分在涂敷的干燥成膜组合物中的结晶，可能有利的是包含抗成核剂。抗成核剂可以适合地选自聚合物，例如聚乙烯醇、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素和羧甲基纤维素。

[0079] 包含于本发明成膜组合物中的活性成分可适合地选自由以下组成的组：维生素 D 衍生物或类似物、皮质类固醇、磷酸二酯酶 4 抑制剂、巨大戟醇衍生物、类视黄醇类诸如阿达帕林、JAK 抑制剂、NK-1 受体拮抗剂、抗生素类如夫西地酸或克林霉素、钙调磷酸酶抑制剂诸如他克莫司或吡美莫司、溶角蛋白剂诸如水杨酸或乳酸、非甾体抗炎剂和局部麻醉剂如利多卡因。

[0080] 维生素 D 衍生物或类似物可选自卡泊三醇、骨化三醇、他卡西醇、马沙骨化醇、帕立骨化醇和阿法骨化醇。优选的已显示在治疗银屑病方面有效的维生素 D 类似物为卡泊三醇。在溶解于推进剂或共溶剂中之前，卡泊三醇可以是无水物或一水合物，优选一水合物的形式。

[0081] 皮质类固醇可选自由安西奈德、倍他米松、布地奈德、氯倍他索、氯倍他松、可的松、地奈德、脱氧可的松、地索米松、地塞米松、二氟可龙、二氟拉松、氟可的松、氟米松、氟尼缩松、醋酸氟轻松、氟轻松、氟米龙、氟泼尼龙、氟氢缩松、氟替卡松、氯氟舒松、卤倍他索、氢化可的松、甲泼尼松、甲基强的松、莫米松、帕拉米松、泼尼卡酯、泼尼松、泼尼松龙和曲安西龙、或其药学上可接受的酯或丙酮化合物组成的组。皮质类固醇可优选选自倍他米松、布地奈德、氯倍他索、氯倍他松、地索米松、二氟可龙、二氟拉松、醋酸氟轻松、氟轻松、氯氟舒松、卤倍他索、氢化可的松、莫米松和曲安西龙或其药学上可接受的酯。皮质类固醇的酯可例如为乙酸倍他米松、二丙酸倍他米松、戊酸倍他米松、丙酸氯倍他索、乙酸地塞米松、氟米松特戊酸酯、丙酸氟替卡松、乙酸氢化可的松、丁酸氢化可的松或糠酸莫米松。丙酮化合物可选自氟轻松丙酮化合物或曲安西龙丙酮化合物。皮质类固醇优选为二丙酸倍他米松或戊酸倍他米松。

[0082] 在目前优选的实施方案中，所述组合物包含卡泊三醇或卡泊三醇一水合物作为维生素 D 类似物以及戊酸倍他米松或二丙酸倍他米松作为皮质类固醇。

[0083] 磷酸二酯酶 4 抑制剂可例如选自公开于 WO 2008/077404、WO2008/104175、WO 2008/128538 或 WO 2010/069322 中的化合物，其公开内容以引用方式包括于本文中。特别优选的磷酸二酯酶 4 抑制剂是 2-{6-[2-[2,3- 二氯吡啶 -4- 基）乙酰基]-2,3- 二甲氧基苯氧基 }-N- 丙基乙酰胺。

[0084] 巨大戟醇衍生物可适合地选自由以下组成的组：巨大戟醇 -3- 当归酸酯、巨大戟醇 -5- 当归酸酯、巨大戟醇 -20- 当归酸酯、20-O- 乙酰基 - 巨大戟醇 -3- 当归酸酯和 20- 脱氧 - 巨大戟醇 -3- 当归酸酯。近来，巨大戟醇 -3- 当归酸酯、也称为巨大戟醇 -3- 甲基丁烯酸酯 (mebutate) 或 PEP 005，已在 US 和 EU 中被批准用于治疗光化性角化病。

[0085] 在具体实施方案中，本发明的成膜组合物包含治疗活性成分和

[0086]

丙烯酸酯/甲基丙烯酸铵共聚物	0.5-1.0%w/w
中链甘油三酯	0.1-0.5%w/w
柠檬酸三丁酯	0.1-0.3%w/w
丁烷	50-60%w/w
二甲醚	40-50%w/w

[0087] 本发明的组合物还可包含常用于皮肤制剂中的其它组分，例如抗氧化剂（例如α-生育酚）、防腐剂、颜料、润肤剂、皮肤舒缓剂、皮肤愈合剂和皮肤调理剂诸如尿素、甘油、尿囊素或红没药醇，参见CTFA Cosmetic Ingredients Handbook，第2版，1992。在优选的实施方案中，所述组合物可以包含抗刺激剂诸如薄荷醇、桉油精或烟酰胺。

[0088] 本发明的组合物可通过向需要此类治疗的患者局部施用有效量的根据本发明的组合物而用于治疗银屑病、脂溢性银屑病、掌跖脓疱病、特应性皮炎、接触性皮炎、湿疹、光化性角化病、瘙痒症、鱼鳞病、酒糟鼻和痤疮以及相关皮肤疾病。所述方法优选包括将治疗上足够剂量的所述组合物局部施用每天一次或两次。为了达到这个目的，根据本发明的组合物优选含有约0.0001-1％w/w的活性成分。可以设想本发明的组合物可有利地用于维持这些皮肤疾病的治疗，即在疾病的可见症状消失后的持续治疗以便延迟症状的复发。本发明的组合物具有用于治疗涉及干燥或片状皮肤的皮肤疾病例如银屑病的额外优势，即油性释放增强剂用作润肤剂可使片状皮肤水化和软化，以得到外观较不干燥的皮肤。

[0089] 在其它方面，本发明涉及适合在患病皮肤区域分配局部组合物的加压容器，该容器包含本发明的组合物和用于释放喷雾形式的组合物的阀组件和致动器。

[0090] 如图6a和6b中所示，适用于加压产品的容器的实例可以包括贮存本发明组合物的容器本体(1)、浸管(2)和包含阀座(3)、阀体(5)和致动器(4)的阀组件。

[0091] 通常情况下，容器本体(1)可以由例如金属、玻璃、陶瓷、聚酯、聚对苯二甲酸乙二醇酯(PET)或其它聚合物等的材料构成。玻璃容器可以具有例如聚丙烯的安全涂层，以容纳被坚硬表面撞击时可能形成的玻璃碎片。金属容器本体是目前优选的，因为其能够较好地耐受撞击，并对表面涂层依从。不锈钢、镀锡铁皮和铝（即铝或铝合金，包括阳极氧化的铝）容器本体是尤其适合于此目的的材料，铝是目前优选的，因为其轻便且不易破损。

[0092] 金属容器通常用惰性物质做内衬或涂层，以保护组合物避免与金属反应，从而阻止或基本上消除组合物中活性成分或其它成分的任何降解。

[0093] 惰性物质包括任何适合的聚合物、漆、树脂或其它在容器和组合物之间制造屏障以防止任何组合物与容器之间的化学相互作用的涂层处理。优选地，该惰性物质是非金属涂层。

[0094] 用于金属容器的已知的涂层包括丙烯酸、酚、聚酯、环氧和乙烯基树脂。但是，包含维生素D的衍生物或类似物的组合物在酸性条件或在酸性反应性化合物存在下容易化学降解。此外，皮质类固醇类已知在碱性条件或在碱性反应性化合物存在下化学降解。因此，用于本发明组合物的涂层应当优选地选择其自身不表现出酸性或碱性反应性、且在组合物存在下不会从其中泄露出酸性或碱性的反应性杂质的容器涂层。

[0095] 已经发现，例如，一种特定的环氧苯酚树脂内部漆与活性成分之一不相容，导致卡

泊三醇发生不可接受的化学降解。此类降解可能源于在漆中存在的松香具有酸性基团。另一方面，当使用聚酰亚胺－聚酰胺树脂作为内部涂层时，卡泊三醇的化学稳定性是令人满意的。

[0096] 除聚酰亚胺－聚酰胺涂层以外，其它适合在金属容器内部做内衬的材料包括聚酰胺、聚酰亚胺、聚丙烯、聚乙烯、氟聚合物，包括聚全氟乙烯丙烯共聚物 (FEP)、氟橡胶 (FPM)、三元乙丙橡胶 (EPDM)、聚四氟乙烯 (PTFE)、乙烯四氟乙烯共聚物 (EFTE)、全氟烷氧基烷烃、全氟烷氧基烯烃，或氟聚合物与非氟碳聚合物的混合物。例如，氟聚合物可以与聚酰亚胺－聚酰胺树脂组合使用。

[0097] 容器涂层材料可以以单层或以多层应用，例如使得每层加工处理后再应用另一层。除了将组合物与金属容器屏蔽以外，应用超过一个涂层还有助于防止活性成分粘附于容器壁上。

[0098] 出于相同的原因，与该组合物接触的容器的阀组件也优选地由不引起该组合物降解的材料构成或者用其涂层。例如，金属阀组件例如阀座可以用阳极氧化的银、环氧三聚氰胺或聚丙烯涂层。

[0099] 同样，为了防止容器泄露，尤其是推进剂泄露，用于该容器内的垫圈或封口的材料也应当优选是化学上惰性的。例如，容器本体和阀座使用中间垫圈叠压在一起，该垫圈至少部分地与组合物接触，因此，如果该垫圈不是由惰性材料构成，其随时间推移可能导致组合物降解。

[0100] 用于在常规气雾剂容器阀中的垫圈材料的广泛检测已经确定，使用含硫加速剂（例如噻唑类）的硫化作用制备的聚合物材料不适合作为用于包含本发明组合物的容器的垫圈材料，可能是因为含硫残余物或杂质与活性成分的一种或两种的反应性导致化学降解。

[0101] 类似地，可渗透入包含于组合物的推进剂中的垫圈材料不适合作为本发明目的的垫圈材料。

[0102] 本发明组合物所用的适合的垫圈或封口材料包括氟橡胶（例如 Viton V600）、氟化乙烯丙烯共聚物 (FEP)、氟橡胶 (FPM，例如 VI500) 或三元乙丙橡胶 (EPDM)。

[0103] 已经发现适合用于浸管的材料是例如聚乙烯和聚丙烯。已经发现适合用于阀杆的材料是例如聚酰胺和乙缩醛 (POM)。

[0104] 在如图 6b 所示的实施方案中，该组合物包含媒介物相 (6)、推进剂相 (7) 和气相 (8)。在该实施方案中，喷雾容器在使用前应当彻底振摇，使得媒介物相 (6) 均匀地悬浮于推进剂相 (7) 中。

[0105] 如图 7 所示，阀组件可以由阀座 (3)（其通常由金属例如铝构成，与容器本体 (1) 经叠压接触），阀体 (5)，其包含与致动器 (4) 连接的阀杆 (51) 和弹簧 (53))，将致动器按压触发以将组合物从容器中排出。该阀杆 (51) 含有至少一个 0.05-1mm 的开孔 (52)，当按压致动器 (4) 时容器中存在的组合物可以通过开孔流出。该阀杆开孔 (52) 可以优选地具有一个球，其使得该容器可以在不同位置例如倒置或斜置下使用。

[0106] 致动器 (4) 具有一个带有直径 0.3-1.5mm 的末端孔口 (41) 的插入物 (44)，通过末端空口排出该组合物。该致动器 (4) 应当设计成能够从孔口 (41) 中提供的气雾剂喷雾具有足够小尺寸的微滴以确保产品的喷雾均匀度，但又足够大以确保组合物的微滴不会在来

自容器的排驱作用下形成细雾，从而导致含有生物活性物质的微滴可能被意外吸入。

[0107] 插入物孔口 (41) 和阀杆开孔 (52) 的尺寸以及容器内的压力通常决定了组合物从开孔 (4) 中排出时所形成的喷雾锥面的宽度，以及由此被喷雾组合物所覆盖的面积大小。

[0108] 在具体的实施方案中，容器可以具有计量该组合物剂量的装置。

[0109] 通过下列实施例进一步阐述本发明，这些实施例不以任何方式限制所要求保护的本发明的范围。

实施例

[0110] 实施例 1

[0111] 组合物

[0112] 制备包括下列成分的参照组合物。

[0113]

聚合物	增塑剂				油	溶剂
	TEC	TBC	DBS	PEG	MCT	乙醇
Klucel LF 5%	X	X	X	X	X	X
Eudragit E 15%	X					X
Eudragit RS 15%	X	X	X	X		X
Dermacryl 79 10%	X				X	X
Dermacryl 79 + Klucel LF					X	X

[0114] TEC：柠檬酸三乙酯

[0115] TBC：柠檬酸三丁酯

[0116] DBS：癸二酸二丁酯

[0117] PEG：聚乙二醇 400

[0118] MCT：中链甘油三酯

[0119] 所述组合物中增塑剂和 / 或油的含量为 20％重量的干燥成膜聚合物。而且，将 1.2％重量的戊酸倍他米松 (1％重量的倍他米松) 加入至所述组合物。

[0120] 为了制备所述媒介物，通过搅拌 1-2 小时将增塑剂 / 油溶解于溶剂中。在搅拌下缓慢加入成膜聚合物，所得混合物搅拌过夜以完成聚合物的溶解。

[0121] 实施例 2

[0122] 组合物

[0123]

成分 (mg/g)	01	02	03	04	05	06
Eudragit RS PO	7.8	7.8	7.8	7.8	7.8	7.8
柠檬酸三丁酯		1.6	0.0	1.6	1.6	0.0

中链甘油三酯			1.6	1.6	3.1	3.1
BDP	1.6	1.6	1.6	1.6	1.6	1.6
丁烷	531.8	531.0	531.0	530.2	529.3	530.2
二甲醚	458.8	458.1	458.1	457.4	456.7	457.4

[0124] 为了制备可喷雾的成膜组合物，将活性成分、增塑剂、油及任选的其它赋形剂称重后装入喷雾容器中，将容器通过插入阀并叠压进行封闭。通过阀加入二甲醚和丁烷，并将容器振摇以溶解在推进剂混合物中的成分。

[0125] 实施例 3

[0126] 实施例 1 的组合物的体外释放试验

[0127] 研究的目的是通过考察针对获得延长的释放特性而对聚合物和增塑剂的类型和浓度的优化，探索聚合物和增塑剂或油性释放增强剂对倍他米松 -17- 戊酸酯 (BMV) 从实施例 1 的组合物的体外释放的影响。这通过测试各种类型和浓度的聚合物和增塑剂来进行，因为这些是预期影响药物从原位形成的聚合物膜中释放的参数。

[0128] 膜：

[0129] Dow **Corning®** 7-4107 硅酮弹性体膜，75 μm。

[0130] 扩散池系统：

[0131] 改进的透析池 (LEO Pharma, 丹麦)。

[0132] 接受室：～ 1.5ml。通过在填充接受室之前和之后对组装的池称重来记录每个池的实际体积。

[0133] 直径：～ 1.55cm，对应于 1.89cm^2的可用的扩散区。

[0134] 将硅酮膜片材切成固定的大小（圆形，**Ø = 22mm**）。将膜置于具有面对供应室的光滑侧的透析池的两个室之间。

[0135] 接受室用预热的接受介质填充（通过称重来记录每个池的实际体积）并且去除可能的气泡。取样臂用塑料塞和 / 或石蜡膜密封以防止接受介质蒸发。用置于接受室中的磁棒将接受相均匀混合。将扩散池置于设定在～ 37℃的加热箱以在膜表面保持～ 32℃的温度。搅拌床设定为 300rpm。使各池平衡最少 30min，然后涂敷 FFS，并开始实验。

[0136] 接受介质：

[0137] 10％ w/w 的在 0.1M 乙酸盐缓冲液 pH 4.5 中的甲基 -β- 环糊精。将接受介质于超声水浴中脱气 20 分钟，然后开始实验，接着在 24h 和 48h 取样。确保低点 (sink) 条件在研究期间一直存在；即，接受相中药物化合物的浓度低于药物在介质中的溶解度的 10％。

[0138] 测试制剂的涂敷、包藏、剂量和体积：

[0139] 使用 Eppendorf 移液管将 240 μl 成膜组合物 (FFC) 轻轻地涂敷并分布在膜表面上 (t = 0h)。移液管在涂敷之前并未去皮重，因为以前的实验显示制剂无显著滞留。这可能部分是溶剂蒸发的结果，使可能的制剂滞留的记录复杂化。记录 240 μl FFC 的重量以用于释放结果的数据处理。由 Eppendorf 移液管递送的 FFC 体积可能由于 FFC 的不同粘度而变化。因此，记录 240 μl FFC 的 10 次连续涂敷的重量（相应的安慰剂制剂用于此目的），

计算平均值且用于释放结果的数据处理。

[0140] 在涂敷 FFC 后将透析池放回到搅拌床上。将池与膜水平地放置，通过阻碍 FFC/ 膜在供应室底部中的蓄积而在溶剂蒸发 / 膜形成期间获得 FFC 的平均分布。

[0141] 暴露和取样时间：

[0142] 以定期的时间间隔从每个池取出 1500 μ l 样品（称重实际体积并记录）。在每次取样后，将接受室用预热的新鲜接受介质重新填充。将取出的样品在 2-8℃储存于密封的 HPLC 小瓶中并避光，直至通过 HPLC 分析进行定量。

[0143] 取样时间点 :0、1、6、24、30、48、54、72h。

[0144] 研究设计：

[0145] 以 3 次重复测试每种制剂 (n = 3)。

[0146] HPLC 分析：

[0147] 根据 130-FKFT-20110614A 规程，于新产品分析部门进行 HPLC 分析。

[0148] 数据分析：

[0149] 为了补充，对分析确定的 BMV 测定值相应地进行修正。将药物浓度转移至电子表格 (Excel) 来计算在 0-72h 时间内累积的释放量。释放率根据累积释放量相对于时间平方根的曲线的线性部分进行计算。根据组中所有各池的数据，计算每个组的平均值和标准偏差 (SD)。

[0150] 结果

[0151] 结果由图 1 和 2 呈现。

[0152] 图 1 显示出与 BMV 从不含增塑剂或油性释放增强剂的成膜组合物的释放相比，在 72 小时的时间内 BMV 从含有 Klucel LF 和 20%（以干燥的成膜聚合物的重量计）的增塑剂 TEC、TBC 和 DBS、或油性释放增强剂 MCT 的成膜组合物的释放。从图 1 可看出，包含增塑剂或油性释放增强剂使活性成分从膜的释放显著增加。

[0153] 图 2 显示出与 BMV 从不含增塑剂或油性释放增强剂的成膜组合物的释放相比，在 72 小时的时间内 BMV 从含有 Eudragit RS PO 和 20%（以干燥的成膜聚合物的重量计）的增塑剂 TEC、TBC 和 DBS、或油性释放增强剂 MCT 的成膜组合物的释放。从图 2 可看出，包含增塑剂或油性释放增强剂使活性成分从膜的释放显著增加。

[0154] 实施例 4

[0155] 实施例 2 的组合物的体外释放试验

[0156] 研究的目的是通过考察针对获得延长的释放特性而对油性释放增强剂浓度的优化，探索聚合物、增塑剂和油性释放增强剂对 BDP 从实施例 2 的组合物中的体外释放的影响。

[0157] 膜：

[0158] Dow **Corning®** 7-4107 硅酮弹性体膜，75 μ m。

[0159] 扩散池系统：

[0160] 改进的透析池 (LEO Pharma, 丹麦)。

[0161] 接受室 :～ 3.75ml。通过在填充接受室之前和之后对组装的池称重来记录每个池的实际体积。

[0162] 直径 : ～ 1.55cm，对应于 1.89cm^2的可用的扩散区。

[0163] 将硅酮膜片材切成固定的大小（圆形，**Ø = 22mm**）。将膜置于具有面对供应室的光滑侧的透析池的两个室之间。

[0164] 通过按压致动器 10 次，将制剂直接喷雾到膜上。

[0165] 接受室用预热和脱气的接受介质填充（通过称重来记录每个池的实际体积）并且去除可能的气泡。取样臂用塑料塞和石蜡膜密封以防止接受介质蒸发。用置于接受室中的磁棒将接受相均匀混合。将扩散池置于设定在～ 37℃的加热箱以在膜表面保持～ 32℃的温度。搅拌床设定为 300rpm。

[0166] 接受介质：

[0167] 10％ w/w 的在 0.05M 乙酸盐缓冲液 pH 4.0 中的甲基 - β - 环糊精。将接受介质于超声水浴中脱气最少 20 分钟，然后开始实验，接着在 24h 和 48h 取样。确保低点条件在研究期间一直存在；即，接受相中药物化合物的浓度低于药物在介质中的溶解度的 10％。

[0168] 乙酸盐缓冲液的成分

[0169]

赋形剂 (g/L)	05P	功能
冰乙酸	2.567	缓冲液
乙酸钠三水合物	0.988	缓冲液
甲基 - β - 环糊精	100	增溶剂
纯水	至 1L	溶剂
NaOH/HCl 适量	至 pH 4.0	

[0170] 乙酸盐缓冲液的制备

[0171] 混合所有赋形剂。用 NaOH 或 HCl 调节 pH 以获得 4.0 的 pH。在 5℃储存缓冲液直至使用。

[0172] 暴露和取样时间：

[0173] 以定期的时间间隔从每个池取出 1500μl 样品（称重实际体积并记录）。在每次取样后，将接受室用预热的新鲜接受介质（与取出体积完全相同的体积！）重新填充。将取出的样品在 2-8℃储存于棕色密封的 HPLC 小瓶中并避光，直至在实验结束时通过 HPLC 分析进行定量。

[0174] 取样时间点：0、1、6、24、30、48、54、72h。

[0175] 研究设计：

[0176] 以 3 次重复测试每种制剂 (n = 3)。

[0177] 样本分析

[0178] 柱：Sunfire C18；3.5μm 或 5μm；150x4.6mm ID 或等价物

[0179] 流动相：乙腈 /0.01M$(NH_4)_2HPO_4$pH 6.4，70:30(v/v)。

[0180] 流速：0.8ml/min

[0181] 检测波长：240nm

[0182] 注射体积：10μl

[0183] 柱温：25℃

[0184] 搁架温度：10℃

[0185] 保留时间 BDP：～ 5.8min

[0186] 运行时间：～ 8min

[0187] 结果

[0188] BDP 累积的释放量（$\mu g/cm^2$）作为时间的函数如图 8 所示。从仅包含成膜聚合物的推进剂驱动的喷雾制剂中观察到最低释放量。加入柠檬酸三丁酯具有释放促进作用，该作用通过加入 0.16% w/w 或 0.31% w/w MCT 作为释放促进剂而进一步增强。

[0189] 实施例 5

[0190] 皮肤亲合性试验

[0191] 通过将包括 1mg/g 的量的色素添加剂（姜黄素）的组合物涂敷于切除的猪耳皮肤上并且在将膜洗涤并干燥之前和之后测定 ΔE 值，来测试实施例 1 的组合物的局部亲合性。ΔE 值是皮肤颜色在洗涤并干燥之前和之后的差异的量度。因此，亲合性的膜导致低 ΔE 值，优选接近于零。

[0192] 5% Klucel LF FFS/20% MCT:

[0193] -ΔE（开始→ 1. 洗涤 / 干燥）= 38

[0194] -ΔE（开始→ 2. 洗涤 / 干燥）= 42

[0195] 15% Eudragit RS PO FFS/20% MCT:

[0196] -ΔE（开始→ 1. 洗涤 / 干燥）= 0.1

[0197] -ΔE（开始→ 2. 洗涤 / 干燥）= 1.2

[0198] 10% Dermacryl 79FFS/20% MCT:

[0199] -ΔE（开始→ 1. 洗涤 / 干燥）= 0.9

[0200] -ΔE（开始→ 2. 洗涤 / 干燥）= 1.5

[0201] ⇨ Klucel<Dermacryl ～ Eudragit

[0202] 亲合性的差异可以归因于所述组合物中使用的成膜聚合物的水溶解度→亲水性的 Klucel 成膜组合物非常容易被洗掉，即具有非常差的亲合性。

[0203] 实施例 6

[0204] 体外皮肤穿透

[0205] 为了研究 BMV 从实施例 1 的组合物的皮肤穿透和渗透，进行皮肤扩散实验。使用来自猪耳的全厚度皮肤用于研究。清洗皮肤并在 -18℃保持冷冻直至使用。在实验前一天，将皮肤置于冷藏库（5±3℃）中以缓慢解冻。

[0206] 具有 3.14cm^2的可用的扩散区和在 8.6 至 11.1ml 范围内的接受体积的静态 Franz 型扩散池基本上以 T. J. Franz, "The finite dose technique as a valid in vitro model for the study of percutaneous absorption in man", 于 Current Problems in Dermatology, 1978, J. W. H. Mall（编）, Karger, Basel, 第 58-68 页中所述的方式使用。测量并记录每个池的具体体积。将磁棒置于每个池的接受室。在安装皮肤后，将生理盐水（35℃）填充入每个接受室以用于皮肤的水化。将池置于热控制的水浴中，该水浴置于设定为 300rpm 的磁力搅拌器上。将水浴中的循环水保持在 35±1℃，以使皮肤表面上的温度为

约 32℃。30min 后，盐水替换为含有 1％甲基 - β - 环糊精的接受介质 15mM 等渗乙酸盐缓冲液 (pH 5.5)。在研究期间一直保持低点条件，即，接受介质中活性化合物的浓度低于化合物在介质中的溶解度的 10％。

[0207] 以 6 个重复测试含有 ^{3}H-BMV 的每种测试组合物的体外皮肤渗透（即 n = 6)。在 0 小时，使用移液管将每种测试组合物涂敷于皮肤膜上。

[0208] 使皮肤渗透实验进行 24 小时。然后在 2、6 和 24h 从下列室收集样品（仅在 24h 对接受介质取样）：

[0209] 移除剩余膜，使用至多 15 个 **D-Squame®** 胶带盘（直径 22mm, CuDerm 公司，Dallas, Texas, USA) 通过胶带剥离 1 次来收集角质层。使用标准压力 10 秒将每个胶带盘施加至测试区，并以一次轻柔的连续移动从测试区移除。对于每个重复胶条，扯掉的方向不同。然后以类似的方式从皮肤上对活的表皮和真皮取样。

[0210] 收集并分析扩散池中剩余的接受室流体的样品 (1ml)。

[0211] 通过液体闪烁计数确定样品中的 ^{3}H-BMV 浓度。

[0212] 结果从下面图 3 看出，显示在 21 小时的过程中 BMV 从所有三种测试组合物穿透，以及 BMV 主要蓄积于角质层中而不是表皮中。从含有 20％（以干燥的成膜聚合物的重量计）MCT 的 Klucel LF 组合物中穿透的 BMV 比从不含增塑剂或油性释放增强剂的 Klucel LF 组合物更多。无 BMV 渗透到接受介质中。

[0213] 实施例 7

[0214] 无毛大鼠体内皮肤穿透

[0215] 研究与实施例 1 中所述的那些类似的但含有二丙酸倍他米松 (BDP ;0.643mg/g) 作为活性成分和 Dermacryl 79（蓝色）、DynamX（红色）和 Eudragit RL PO（绿色）作为成膜聚合物的组合物在 7 天时间内对无毛大鼠皮肤的穿透。倍他米松软膏剂（紫色）用作对比制剂。

[0216] OFA-hr/hr 株系的雄性无毛大鼠获自 Charles River, USA。

[0217] 在研究开始之前对大鼠称重。在异氟烷麻醉下，将 100μl 制剂涂敷至每只鼠背部上的 4x3cm 区域。将大鼠放置 2 分钟以使制剂干燥，并将 Optiskin 膜 (5.3x7.2cm, URGO Laboratories, 法国）覆盖于该区域上，其上覆盖 Fixomull stretch (BSN Medical, 德国)。

[0218] 在给药后 24h 从各组将要处死的动物中收集舌下血样。在给药后 30min、2h、4h 和 6h 采集样品。

[0219] 在给药后 24h 或 7 天处死动物。在处死之前从每只动物采集舌下血样。大鼠用 CO_2 安乐死。从涂敷的皮肤区域采集皮肤活组织检查的样品。将皮肤用浸泡于 99.9％乙醇中的薄纸轻轻清洗。将活检样品称重并保持 -80°直至定量分析。

[0220] 通过 LC 质谱法确定样品中 BDP 或倍他米松的浓度。

[0221] 结果从下面图 4 和 5 呈现。

[0222] 图 4 显示在 1 天和 7 天后 BDP 及其代谢物倍他米松的皮肤浓度，由此可看出，1 天后的皮肤穿透在含有 DynamX 作为成膜聚合物的成膜组合物中是最高的，并且与涂敷对比软膏剂相比，含有 DynamX 或 Eudragit RL PO 作为成膜聚合物的成膜组合物的涂敷导致更高的活性成分穿透。可进一步看出，在涂敷含有 Dermacryl 79 或 DynamX 的成膜组合物后，

BDP 和 / 或倍他米松在皮肤中保持 7 天。

[0223] 图 5 显示了涂敷成膜组合物和对比软膏剂后在 24h 内倍他米松的血清浓度。可看出，涂敷软膏剂会导致渗透通过皮肤，而在涂敷成膜组合物后在血清中几乎没有发现倍他米松。

[0224] 实施例 8

[0225] 无毛豚鼠皮肤的体内穿透

[0226] 该项研究的目的是研究在无毛豚鼠的侧腹部施用实施例 2 的成膜组合物 1、2、4 和 5 后，历经延长的时间周期（7 天）二丙酸倍他米松在皮肤中的药代动力学。

[0227] 该项研究是在 12 只雌性 IAF 无毛豚鼠 (Crl:HA-Hr^{hr}获自 Charles River) 中进行。将动物按照 LEO Pharma 的标准程序圈养。

[0228] 给药前，将动物用氯胺酮 50mg/kg 和赛拉嗪 5mg/kg 腹膜内注射 (1.25ml/kg) 麻醉。

[0229] 按照以下日程表通过喷雾施用组合物，并通过带有圆形孔（18mm 直径）的滤纸的给药板喷雾以控制给药面积。全部制剂都通过喷雾 5 次来施用。

[0230]

日期	动物编号	RB Tx 区域	RF Tx 区域	LB Tx 区域	LF Tx 区域
2013-06-13	1	1	2	4	5
2013-06-13	2	5	4	2	1
2013-06-13	3	3	4	1	2
2013-06-17	4	1	2	4	5
2013-06-17	5	5	4	2	1
2013-06-17	6	4	5	1	2
2013-06-19	7	1	2	4	5
2013-06-19	8	5	4	2	1
2013-06-19	9	4	5	1	2
2013-06-20	10	1	2	4	5
2013-06-20	11	5	4	2	1
2013-06-20	12	4	5	1	2

[0231] 施用组合物后，有规律地观察动物。观察参数是：

[0232] 在给药位点的局部皮肤反应、由制剂引起的任何不适或刺激的行为指征、制剂的可见残余物。

[0233] 在 2013-06-20 星期四处理的动物在处理后 2 小时处死。

[0234] 将每只动物用氯胺酮 50mg/kg 和赛拉嗪 5mg/kg 腹膜内注射 (1.25ml/kg) 麻醉，并通过将动物在 CO_2 中窒息安乐死。

[0235] 每个检测位点都用浸湿的棉花轻轻擦拭两次以除去任何过量的制剂，并在每个位点钻取一处 4mm 活组织进行检查。随后，使用 D-Squame 胶带将处理位点进行胶带剥离 (tape stripped) 20 次。将胶带剥离条保存用于分析。胶带剥离后从每个位点钻取一处 4mm 活组织进行检查。将该活组织转移至 DMPK 以分析组织浓度。

[0236] 经 LC-MS/MS 的生物分析在 DMPK&Safety 中进行。简言之，用乙醚从皮肤活组织中提取二丙酸倍他米松。蒸发乙醚，并将残余物在包含作为内标物的氘代二丙酸倍他米松的甲醇：水 (50:50) 中重构。使用乙腈提取胶带剥离条。

[0237] 使用 AB Sciex API 5000 分析样品。

[0238] 结果

[0239] 样品中 BDP 的量对面积变异进行校正并以 $\mu g/cm^2$ 表达。

[0240] 胶带剥离条中的全部组合物在较早时间点 (2h、24h) 比较晚时间点显示更高的 BDP 的量。来自用制剂 2 处理的区域的胶带剥离条显示最高的二丙酸倍他米松的量。

[0241] 来自胶带剥离的皮肤的结果如图 9 所示。经过胶带剥离的皮肤显示 BDP 的量较低，反映出大部分剂量留存于胶带剥离条中。但是，用制剂 4 处理的皮肤随时间在皮肤中的量具有不显著的减少。这可能表明相对于其它制剂而言从制剂 4 中延长释药。在 1-3 天后，用制剂 2 处理的皮肤显示在胶带剥离的皮肤中含量最高，但在 7 天后，用制剂 1 和 2 处理的皮肤显示二丙酸倍他米松的量近似。由于在用制剂 5 处理的胶带剥离的皮肤样品分析中的高变异性，该制剂的数据未列出。

[0242] 经观察，完整皮肤比胶带剥离的皮肤显示更高的 BDP 的量 (数据未出示)。这反映出大部分剂量留存于角质层的事实。用制剂 2 处理的皮肤显示最高的化合物量，且用制剂 1、4 和 5 处理的皮肤显示较低的量。

[0243] 在胶带剥离条和在未进行剥离的皮肤中 BDP 的量是近似的，反映出大部分剂量留存于角质层的事实。制剂 2 显示在较早时间点的两种样品类型中的量最高。

[0244] 已进行胶带剥离的皮肤显示出低的 BDP 量。在 1-3 天后，用制剂 2 处理的皮肤显示在胶带剥离条中含量最高，但在 7 天后，用制剂 1 和 2 处理的皮肤显示二丙酸倍他米松的量近似。但是，用制剂 4 处理的皮肤在皮肤中的量作为时间的函数具有不显著的减少。这可能表明相对于其它制剂而言从制剂 4 中延长释药。

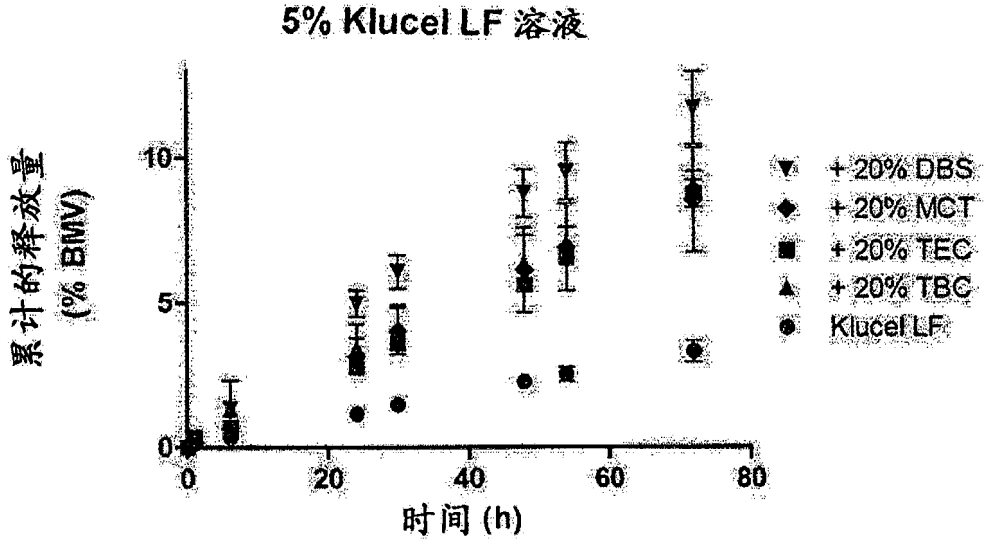

5% Klucel LF 溶液
累计的释放量 (% BMV)
0
5
10
0
20
40
60
80
时间 (h)
+ 20% DBS
+ 20% MCT
+ 20% TEC
+ 20% TBC
Klucel LF

图 1

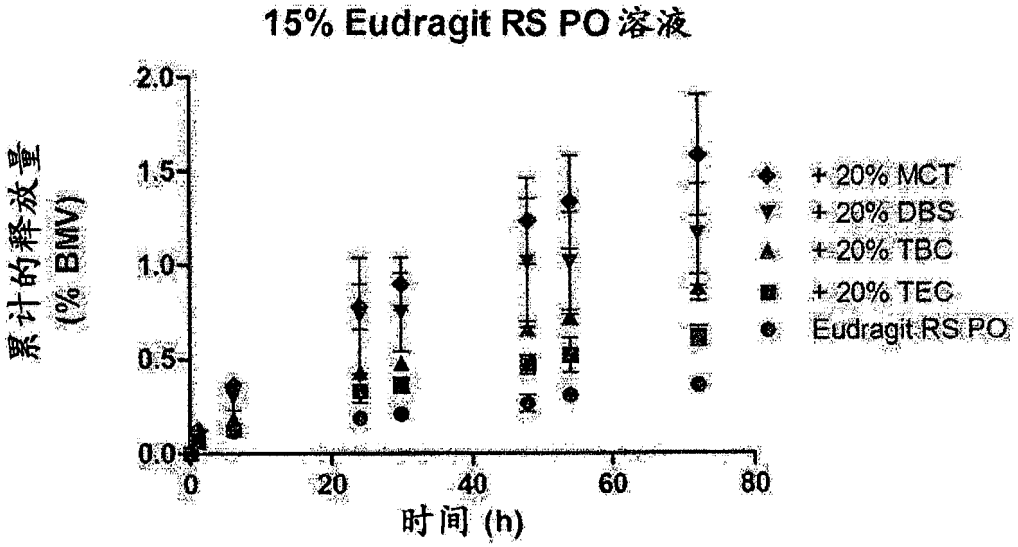

15% Eudragit RS PO 溶液
累计的释放量 (% BMV)
0.0
0.5
1.0
1.5
2.0
0
20
40
60
80
时间 (h)
+ 20% MCT
+ 20% DBS
+ 20% TBC
+ 20% TEC
Eudragit RS PO

图 2

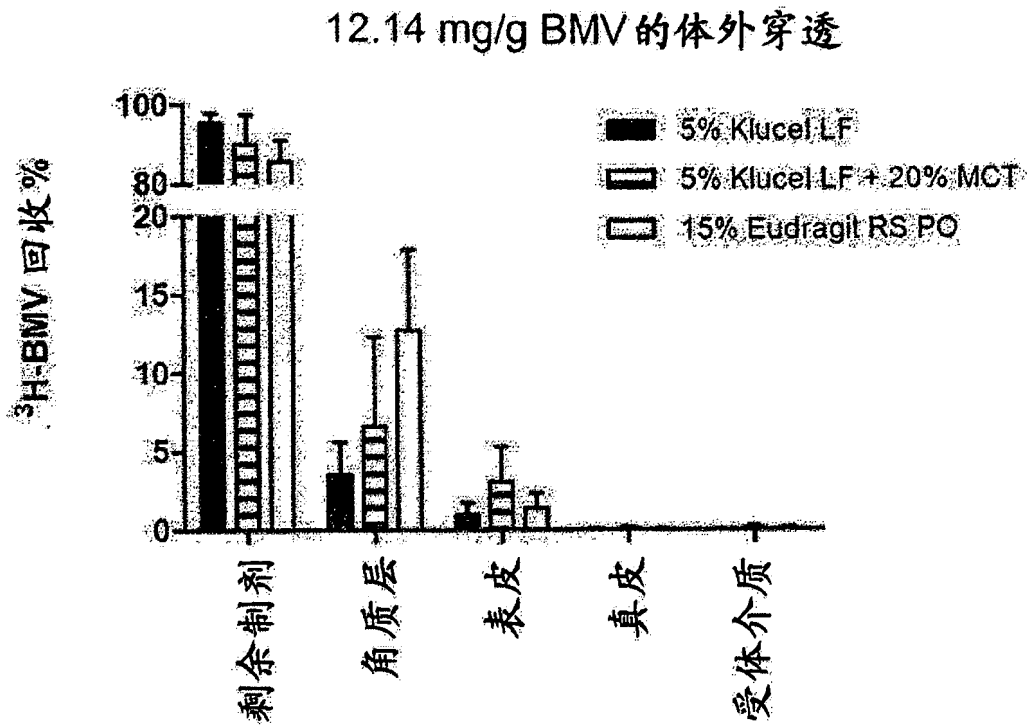

12.14 mg/g BMV的体外穿透
^{3}H-BMV 回收%
100
80
20
15
10
5
0
5% Klucel LF
5% Klucel LF + 20% MCT
15% Eudragit RS PO
剩余制剂
角质层
表皮
真皮
受体介质

图 3

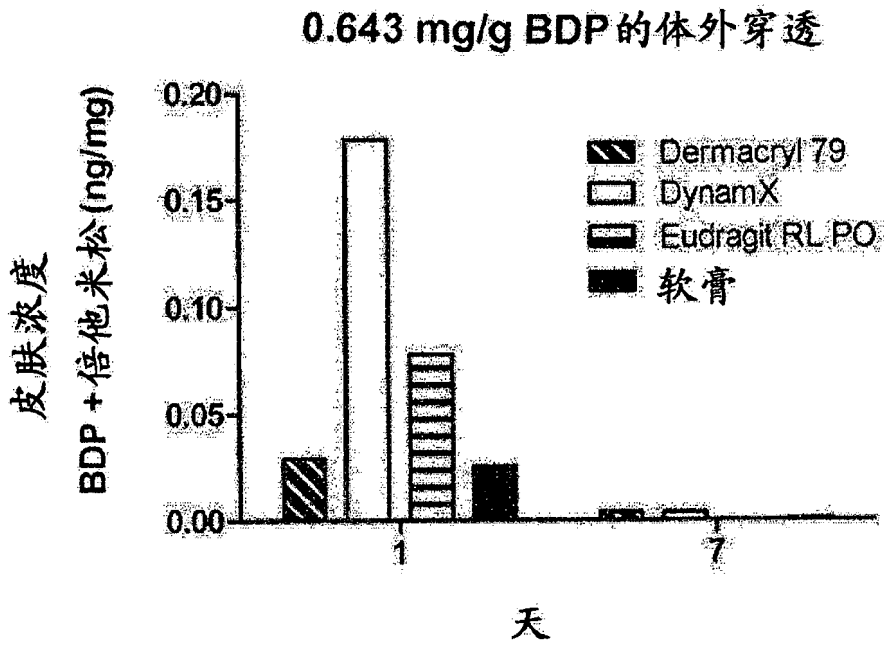

0.643 mg/g BDP的体外穿透
皮肤浓度
BDP + 倍他米松(ng/mg)
0.20
0.15
0.10
0.05
0.00
1
7
天
Dermacryl 79
DynamX
Eudragit RL PO
软膏

图 4

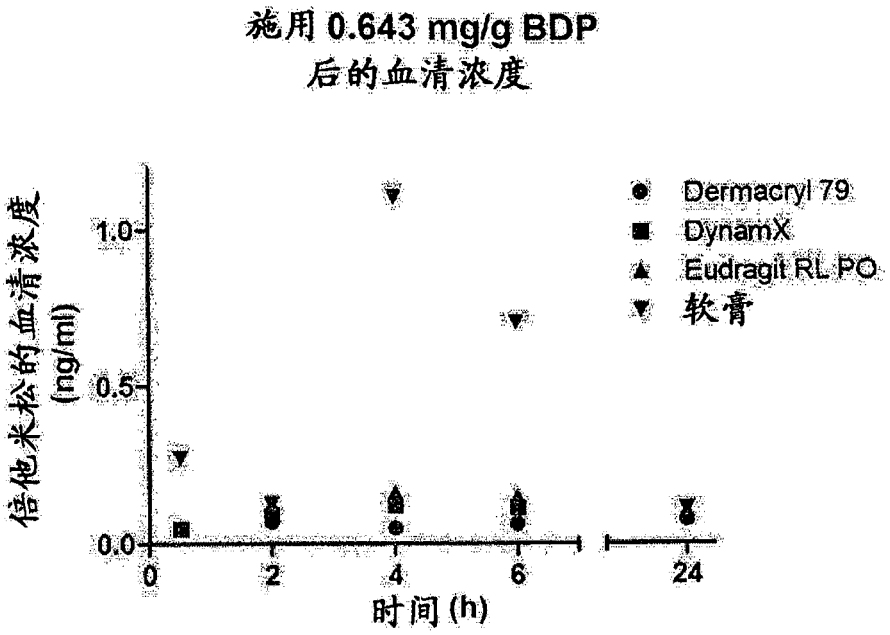

施用 0.643 mg/g BDP
后的血清浓度
倍他米松的血清浓度
(ng/ml)
1.0
0.5
0.0
0
2
4
6
24
时间 (h)
Dermacryl 79
DynamX
Eudragit RL PO
软膏

图 5

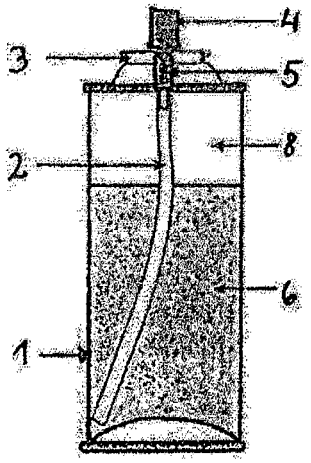

4
3
5
8
2
6
1

图 6a

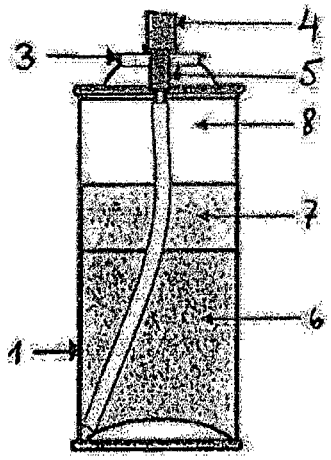

4
3
5
8
7
6
1

图 6b

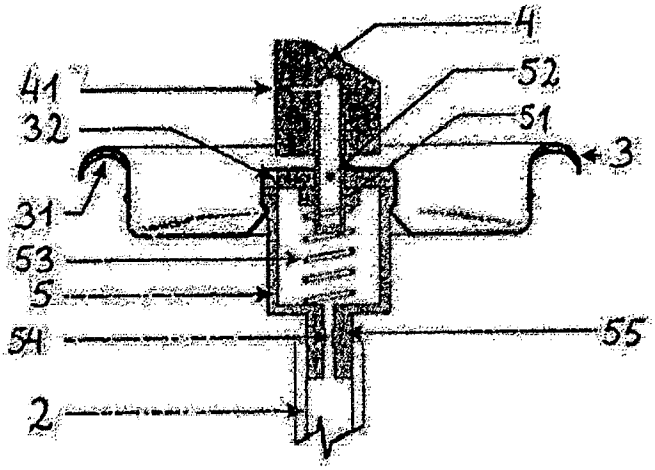

4
41
52
32
51
3
31
53
5
5H
55
2

图 7

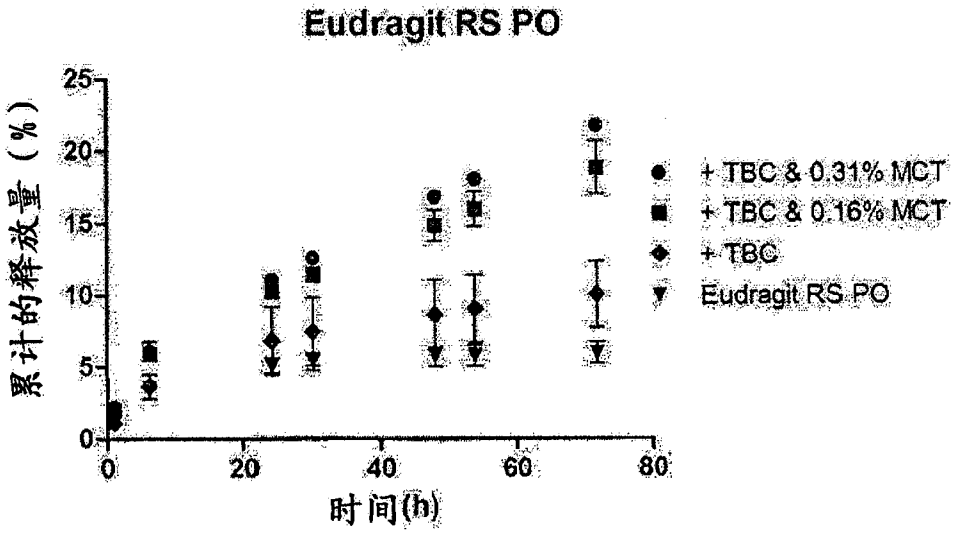

Eudragit RS PO
累计的释放量（%）
25
20
15
10
5
0
0
20
40
60
80
时间(h)
+ TBC & 0.31% MCT
+ TBC & 0.16% MCT
+ TBC
Eudragit RS PO

图 8

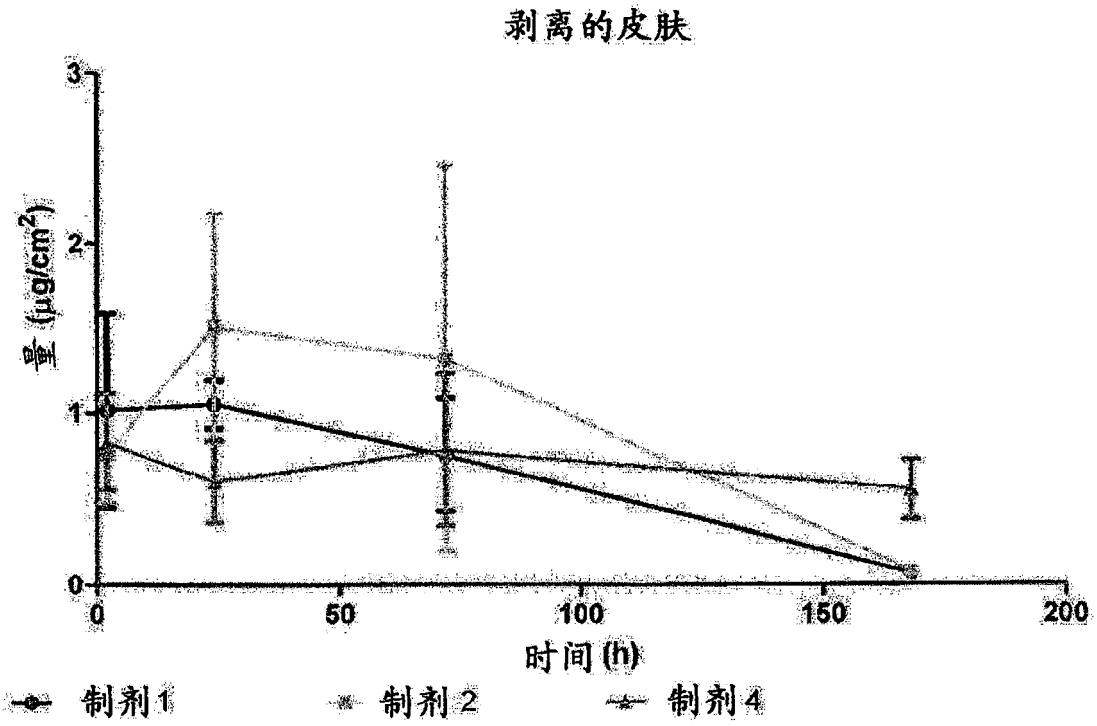


图 9

Abstract

A sprayable film-forming pharmaceutical composition for dermal application comprises at least one therapeutically active ingredient dissolved in a pharmaceutically acceptable propellant selected from the group consisting of dimethyl ether, diethyl ether and methylethylether, and a mixture of dimethyl ether, diethylether and methylethyl ether, and a second propellant selected from C_{3-5} alkanes, hydrofluoroalkanes, hydrochloroalkanes, fluoroalkanes and chlorofluoroalkanes, the propellant being present in an amount of 50-99.5% w/w of the composition, the composition further comprising a film-forming polymer, a plasticizer and an oily release-enhancing agent.