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DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] The present invention is in the field of pharmacotherapy. More specifically, it relates to the treatment of diseases and conditions affecting the skin and skin appendages.

[0002] The pharmacological treatment of cutaneous disorders may involve systemic or local administration of an effective medicament. Typically, whenever local (e.g. epicutaneous) administration is possible and leads to the desired outcome, it is preferred over systemic therapy which is, quite plausibly, more often associated with adverse systemic effects. However, effective treatment via the topical route of administration requires that the drug substance is soluble in, and/or otherwise compatible with a suitable carrier or vehicle, and that it reaches its target tissue layer(s) in an effective amount or concentration. In fact, in some cases, effective epicutaneous treatment is particularly difficult to achieve.

[0003] The skin consists of three main layers - the epidermis, the dermis and the hypodermis. The epidermis comprises the stratum corneum (the outermost superficial layer of skin, consisting of dead cells) and the vital (living) epidermis. Depending on the cutaneous disease or condition, one or more layers of the skin may become affected. In some dermatological conditions, such as ichthyosis, callus, or plaque psoriasis, the stratum corneum is thicker than in the healthy state and can provide a significantly greater barrier to the penetration of a therapeutical compound, thus reducing its efficacy in the treatment of the deeper layers of the skin. Moreover, it has been shown recently that with increasing age, the skin of a human also becomes more resistant to the penetration by drug substances.

[0004] The use of penetration enhancers has been proposed in order to achieve a sufficient and consistent availability of various therapeutic compounds at the site of action during the treatment of cutaneous diseases. For example, U.S. Patent No. 5,326,566 describes a composition of a pharmacological agent in combination with dibutyl adipate, or a mixture of dibutyl adipate and isopropyl myristate, which could enhance the penetration through the skin and even increase the amount absorbed into the systemic circulation, if that is desired.

[0005] Even though a variety of penetration enhancers have been used for enhancing the absorption of therapeutic agents into and through the skin, substantial problems may arise when the penetration enhancers are incompatible with a particular drug substance, leading to drug instability and degradation into potentially harmful degradants.

[0006] US 2005/0079210 A1 proposes the use of liposomes the epicutaneous administration of drugs and cosmetically useful agents. However, liposomes are difficult to manufacture cost-effectively and in a reproducible manner.

[0007] Other novel formulation strategies for topical medications require the occlusion of the skin after administration, which is however perceived as inconvenient by many patients

[0008] EP0670159A1 discloses stable oily emulsions comprising surfactant and semifluorinated alkane, which are proposed to be suitable for transporting oxygen to the skin or vascular system or for use as a standard for blood-gas analysis. The use of these compositions as carriers of active agent was also suggested, although no mention is made of whether these compositions are capable of effectively delivering active agents in particular to the deeper layers of the skin.

[0009] There clearly remains a need for pharmaceutical formulations and vehicles which allow the effective treatment of cutaneous disorders by topical administration. It is therefore an object of the present invention to provide such improved compositions which overcome one or more disadvantages of known compositions. In particular, it is an object of the invention to provide compositions of topically active drug substances which are effective and convenient. Further objects of the invention will become clear on the basis of the description of the invention below, including the examples, and of the patent claims.

SUMMARY OF THE INVENTION

[0010] The present invention provides a novel pharmaceutical composition for administration to the skin or a skin appendage. The composition comprises an effective amount of an active ingredient and a semifluorinated alkane (SFA) according to formula RFRH, wherein RF is a linear perfluorinated hydrocarbon segment with 4 to 12 carbon atoms, and RH is a linear alkyl group with 4 to 8 carbon atoms; wherein the active ingredient is an anti-infective selected from azithromycin, erythromycin, clindamycin, or

minocycline, where the composition is for use in treating or preventing acne; or wherein the active ingredient is a macrolide immunosuppressant selected from tacrolimus, sirolimus, everolimus, pimecrolimus, ridaforolimus, temsirolimus, zotarolimus, and ciclosporin A, where the composition is for use in the treatment or prevention of psoriasis. In a preferred embodiment, the SFA is selected from F4H5, F4H6, F4H8, F6H6 and F6H8.

[0011] It has been surprisingly found by the inventors that SFAs are capable of delivering active pharmaceutical ingredients effectively into the deeper layers of the skin, i.e. into the vital layers below the stratum corneum of the epidermis. Moreover, they are capable of delivering active ingredients deep into nails.

[0012] The composition may, for example, be in the form of a solution or an emulsion. They are useful for administering a wide range of topical agents indicated in a number of cutaneous diseases and conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013]

Figure 1 shows the amount of tacrolimus found in different layers of the skin (SC=stratum corneum; EP=vital epidermis; DR=dermis; AK=hypodermis) 30 min, 300 min, and 1,000 min after administration as an SFA-based formulation to human skin, relative to the administered dose. For further details, see Example 1.

Figure 2 shows the amount of tacrolimus found in different layers of the skin (SC=stratum corneum; EP=vital epidermis; DR=dermis; AK=hypodermis) 30 min, 300 min, and 1,000 min after administration of a commercial formulation (Protopic® 0.1%) to human skin, relative to the administered dose. For further details, see Example 1.

Figure 3 shows the penetration profiles of tacrolimus 30 min, 300 min, and 1,000 min after administration as an SFA-based formulation to human skin, respectively. For further details, see Example 1.

Figure 4 shows the penetration profiles of tacrolimus 30 min, 300 min, and 1,000 min after administration a commercial formulation (Protopic® 0.1%) to human skin, respectively. For further details, see Example 1.

Figure 5 shows the concentration of D,L- α -tocopherol found in different layers of the skin (SC=stratum corneum; EP=vital epidermis; DR=dermis) 100 min after administration as SFA-based formulation (SFA), Unguentum emulsificans aquosum DAB (WHS), Basiscreme DAC (BC), Lanae alcoholum unguentum aquosum DAB (WWS). For further details, see Example 2.

Figure 6 shows the concentration of betamethasone-17,21-dipropionate in different layers of the skin (SC=stratum corneum; EP=vital epidermis; DR=dermis) 100 min after administration as SFA-based formulation (SFA), Unguentum emulsificans aquosum DAB (WHS), Basiscreme DAC (BC), Lanae alcoholum unguentum aquosum DAB (WWS). For further details, see Example 3.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The invention provides a novel pharmaceutical composition for use as a topical formulation which is to be administered to the skin or a skin appendage. The composition comprises an effective amount of an active ingredient selected from tacrolimus, sirolimus, everolimus, pimecrolimus, ridaforolimus, temsirolimus, zotarolimus and ciclosporin A, where the composition is for use in the treatment or prevention of psoriasis, or an anti-infective selected from azithromycin, erythromycin, clindamycin, or minocycline, where the composition is for use in the treatment or prevention of acne; and a semifluorinated alkane according to formula RFRH, wherein RF is a perfluorinated hydrocarbon segment with 4 to 12 carbon atoms and RH is a linear non-fluorinated hydrocarbon segment with 4 to 8 carbon atoms.

[0015] The invention is based on the surprising discovery that the semifluorinated alkanes (SFAs) as defined above are highly suitable carriers for topically administered drugs and capable of delivering such drugs very effectively to the layers of the skin below the stratum corneum, i.e. the viable epidermis, but also to the dermis and hypodermis. This was particularly unexpected in view of Hardung (Doctoral Thesis, Albert-Ludwigs-University of Freiburg, Germany, 2008), who investigated the suitability of SFAs as carriers for topical medications using e.g. testosterone as a model drug, and who came to the conclusion that an SFA such as F6H8 (see below for an explanation of the terminology of SFAs) does not affect an improved penetration into the skin, interact with the stratum corneum or exhibit any penetration-enhancing effect (p. 103, first full paragraph). However, in spite of such

discouraging statements in the prior art, the inventors have further investigated the impact of SFAs and SFA-based carriers on the delivery of drugs into the deeper layers of the skin and nails using excised human skin (in contrast to Hardung who used pig skin), and have now surprisingly found that SFAs are indeed capable of enhancing the penetration of drugs into the relevant skin layers, as will be shown in more detail below.

[0016] As used herein, a pharmaceutical composition is any composition comprising an active ingredient useful for the diagnosis, prevention, management or therapy of a disease, symptom or health condition and at least one carrier or excipient. A topical formulation is a composition which is in a form suitable for topical administration. In the present invention, the composition is suitable for administration to the skin or a skin appendage of a subject, which subject may be a human or an animal. The skin may be intact skin or injured, bruised, damaged or otherwise affected skin. A skin appendage is a structure derived from the skin, and usually adjacent to it, such as a hair, a sweat or sebaceous gland. Semifluorinated alkanes are linear or branched alkanes some of whose hydrogen atoms have been replaced by fluorine. The semifluorinated alkanes (SFA's) used in the present invention are composed of at least one non-fluorinated hydrocarbon segment and at least one perfluorinated hydrocarbon segment. The SFA's have one non-fluorinated hydrocarbon segment attached to one perfluorinated hydrocarbon segment, according to the general formula $F(CF_2)_n(CH_2)_mH$.

[0017] Another nomenclature which is used herein refers to the above-mentioned SFA's having two segments as RFRH, wherein R_F designates a perfluorinated hydrocarbon segment, R_H designates a non-fluorinated segment. Alternatively, the compounds may be referred to as F_nH_m and F_nH_mF_o, respectively, wherein F means a perfluorinated hydrocarbon segment, H means a non-fluorinated segment, and n, m and o is the number of carbon atoms of the respective segment. For example, F3H3 is used for perfluoropropylpropane. Moreover, this type of nomenclature is usually used for compounds having linear segments. Therefore, unless otherwise indicated, it should be assumed that F3H3 means 1-perfluoropropylpropane, rather than 2-perfluoropropylpropane, 1-perfluoroisopropylpropane or 2-perfluoroisopropylpropane.

[0018] SFAs are also described in EP-A 965 334, EP-A 965329 and EP-A 211126.

[0019] The perfluorinated segment is linear and comprises from 4 to 12 carbon atoms, and/or the non-fluorinated segment is linear and comprises from 4 to 8 carbon atoms. Preferred SFA's include in particular the compounds F4H5, F4H6, F4H8, F6H4, F6H6, F6H8, and F6H10. Presently most preferred for carrying out the invention are F4H5, F4H6, F6H6 and F6H8.

[0020] Optionally, the composition may comprise more than one SFA. It may be useful to combine SFA's, for example, in order to achieve a particular target property such as a certain density, viscosity, or solubilising capacity for a particular active ingredient. If a mixture of SFA's is used, it is furthermore preferred that the mixture comprises at least one of F4H5, F4H6, F4H8, F6H4, F6H6, F6H8, and F6H10, and in particular one of F4H5, F4H6, F4H8, F6H6 and F6H8. In another embodiment, the mixture comprises at least two members selected from F4H5, F4H6, F4H8, F6H4, F6H6, F6H8, and F6H10, and in particular at least two members selected from F4H5, F6H6, F4H8, and F6H8. Furthermore, mixtures of a semifluorinated alkane, e.g. F4H5, with a perfluorinated compound, such as perfluorooctylbromide or perfluorodecalin, or with another oily material are also contemplated. Other oily materials would, for example, include silicone oils, triglycerides (e.g. native or synthetic medium-chain triglycerides), or compounds such as isopropyl myristate. In some preferred embodiments, however, perfluorinated compounds are absent.

[0021] Liquid SFA's are chemically and physiologically inert, colourless and stable. Their typical densities range from 1.1 to 1.7 g/cm³, and their surface tension may be as low as 19 mN/m. SFA's of the RFRH type are insoluble in water but also somewhat amphiphilic, with increasing lipophilicity correlating with an increasing size of the non-fluorinated segment. Again, for practising the current invention, an SFA having a density of at least 1.2 g/cm³ should be selected.

[0022] Liquid SFA's of the RFRH type are being used commercially for unfolding and reapplying a retina, for long-term tamponade as vitreous humor substitute (H. Meinert et al., European Journal of Ophthalmology, Vol. 10(3), pp. 189-197, 2000), and as wash-out solutions for residual silicon oil after vitreo-retinal surgery. Experimentally, they have also been used as blood substitutes (H. Meinert et al., Biomaterials, Artificial Cells, and Immobilization Biotechnology, Vol. 21(5), pp. 583-95, 1993). These applications have established SFA's as physiologically well tolerated compounds. On the other hand, SFA's have not been used as excipients in approved drug products as of today.

[0023] For allowing convenient administration to the skin or skin appendages, the composition is preferably liquid or semi-solid. As used herein, semi-solid means that a material behaves like a solid upon the exertion of low shear force, but above a certain force threshold, the so-called "yield point", it behaves like a viscous fluid. Whether liquid or semi-solid, the composition may represent a single phase (i.e. a solution), or consist of two or more phases.

[0024] In a particular embodiment, for example, the composition is in the form of an emulsion. As used herein, an emulsion is a system comprising a dispersed (or inner, or emulsified, or discontinuous) liquid phase within a continuous (or outer, or coherent) liquid or semisolid phase. The two phases are not miscible. In an O/W-emulsion (also referred to as oil-in-water emulsion), a water-immiscible organic liquid phase, which does not have to be an "oil" by any specific definition, is dispersed in a water-miscible continuous phase which may or may not be substantially comprised of water itself. Within emulsions, O/W-emulsions are preferred for carrying out the invention.

[0025] In another embodiment, the composition is in the form of a microemulsion. A microemulsion is a clear, thermodynamically stable, optically isotropic mixture of a lipophilic component, a hydrophilic component, and an amphiphilic component. Typically, a microemulsion forms spontaneously when the components are combined and mixed with each other, without requiring high energy input as is normally required for the formation of an "ordinary" emulsion. Microemulsions may have a colloidal lipophilic phase dispersed in a hydrophilic phase, or a hydrophilic phase colloiddally dispersed in a lipophilic phase. The size of the dispersed phases is usually in the range from about 5 nm to about 400 nm, and most often below about 200 nm. In one of the preferred embodiments of the invention, the particle size is from about 5 nm to about 100 nm. In terms of its rheological properties, the microemulsion may be in the form of a liquid or a gel, i.e. in liquid or semisolid form. In a preferred embodiment, the microemulsion is in liquid form.

[0026] For microemulsions according to the invention, it is preferred to use an oil phase comprising from about 5 to about 95 wt.-% of SFA, and more preferably from about 10 to about 80 wt.-% of SFA, the remainder of the oil phase being another oil such as isopropylmyristate. With respect to the incorporation of aqueous components, surfactants and optionally cosurfactants, commonly known constituents of microemulsions may be used to formulate the composition.

[0027] The composition, whether formulated as a solution, microemulsion or conventional emulsion, may contain any further pharmaceutically acceptable ingredients as required or useful in view of the intended application. In a particular embodiment, an additional solvent or co-solvent may be incorporated, for example in order to achieve a higher solubility for a specific active ingredient, to modify the viscosity or stability of the formulation, or to further enhance the cutaneous penetration of the active ingredient. Such co-solvent should of course be selected in type, quality and amount such as to maintain the physiological tolerability of the formulation. Potentially suitable co-solvents include ethanol, acetone, ethyl acetate, isopropyl alcohol, glycerol, propylene glycol, pentylene glycol, polyethylene glycol, liquid paraffin, triglyceride oils, hydrofluorocarbons such as HFA 134a and/or HFA 227, and liquid mono- or diglycerides. Among these, ethanol and pentylene glycol are among the particularly preferred solvents. It has been found that relatively small amounts of ethanol may substantially modify the solubilising properties of SFAs and allow the incorporation of a number of active ingredients at higher concentrations. For example, the composition may comprise up to about 10 wt.-% of ethanol, or up to about 5 wt.-% of ethanol. Even at a low concentration of up to about 3 wt.-%, ethanol may be a very useful additive in the composition, depending on the specific drug substance to be delivered. Pentylene glycol is also very useful as co-solvent in general and, in particular, it has been found that its incorporation is advantageous in the formulation of microemulsions.

[0028] Moreover, the composition may comprise one or more stabilisers, surfactants (in particular if the composition is in the form of an emulsion or microemulsion), cosurfactants (in particular if it is in the form of a microemulsion), colouring agents, antioxidants (for example, α -tocopherol), thickeners (viscosity-increasing agents such as bentonite), and fragrances.

[0029] If a surfactant is present, it may, for example, be selected from physiologically acceptable phospholipids (such as phosphatidylcholines); nonionic surfactants such as fatty alcohols, pegylated glycerides, pegylated fatty acids, pegylated fatty alcohols, pegylated sorbitan fatty acid esters, and poloxamers; anionic surfactants such as sodium lauryl sulphate, docusate sodium, and sodium deoxycholate.

[0030] The composition may be prepared by commonly known techniques for the manufacture of pharmaceutical solutions, emulsions, and microemulsions. Depending on their consistency and specific use, they may be presented in bottles, spray bottles, or tubes.

[0031] The active ingredient is selected from drug substances useful for the prevention and in particular for the management and therapy of psoriasis or acne. The invention appears generally useful for delivering drug substances to the deep layers of the skin, i.e. to the vital epidermis, the dermis, and/or to the hypodermis which may also be understood as being part of the integumentary system. Topical administration of the compositions to the skin may result in the delivery of the drug substance to the stratum corneum, as well as penetration through the stratum corneum and delivery of the active drug substance to these deeper skin layers. Cutaneous diseases or conditions may affect the stratum corneum, as well as one or more of the deeper skin layers. The composition is used in the therapy of psoriasis, and incorporates a macrolide immunosuppressant, selected from tacrolimus, sirolimus, everolimus, pimecrolimus, ridaforolimus, temsirolimus, zotarolimus, and ciclosporin A. Tacrolimus is one of

the particularly preferred drugs in this group. It has been found by the inventors that tacrolimus can be very effectively (i.e. faster and deeper than using conventional formulations) delivered to the deep and viable layers of the skin using the composition of the invention (see Example 1).

[0032] As illustrated in Example 1, the composition of the invention may be used to effectively deliver an active ingredient such as a macrolide immunosuppressant, as for example tacrolimus, to the deeper layers of the skin. For example, at least about 5% of the topically administered amount of drug may be delivered to the vital epidermis within only about 30 minutes. The composition may also be used to deliver at least 5% of the topically administered drug to the dermis within about 30 minutes, or even at least about 10% of the administered dose. Also in terms of delivery to the hypodermis, the composition may be used to deliver at least 5% of the topically administered amount of drug to this layer within the same period of time, or even 10% or more.

[0033] Taking into account the typical thickness of the respective skin layers, the composition may be used to deliver within about 30 minutes at least about 15% of the topically administered drug dose to a depth of at least about 10 μm . In other embodiments, at least about 20% of the dose is delivered to a depth of at least about 10 μm . The composition may also be used to deliver at least about 10% of the topically administered drug to a depth of 100 μm or more within about 30 minutes; or at least about 15% or at least about 20% of the dose, respectively.

[0034] In a further embodiment, the disease to be treated is acne, such as acne vulgaris or other forms of acneiform eruptions. In this case, the active ingredient is selected from the antiinfective agents azithromycin, erythromycin, clindamycin, or minocycline.

[0035] The invention is further illustrated by the following examples.

Examples

Example 1

[0036] Tacrolimus was dissolved in a liquid carrier comprising F6H8 and 3.8 wt.-% ethanol to obtain a clear solution having a tacrolimus concentration of 1 mg/mL.

[0037] Excised human skin was obtained from a breast reduction surgical centre. Skin samples were washed with isotonic sodium chloride solution. The subcutaneous adipose layers were removed. Circular pieces of 20 mm in diameter (3.14 cm^2) were punched out, supported by filter gauze, and mounted in FRANZ diffusion cells in such a way that the dermal side was in contact with the acceptor fluid (PBS pH 7.4), which was continuously stirred and kept at 32 °C. Loss through evaporation was avoided by means of a glass lid.

[0038] On each skin sample (epidermal side), an amount of 20 μL of the tacrolimus solution was placed and spread out evenly. After a testing time of 30 min, 300 min, or 1,000 min, respectively, the remaining tacrolimus solution on the samples was collected and the skin samples were removed. From each specimen, three small punch biopsies of 6 mm diameter (0.2827 cm^2) were obtained and frozen. At -40 °C, the punch biopsies were cryomicrotomed as follows:

- 1 slice of 10 μm thickness, corresponding to the stratum corneum
- 4 slices of 20 μm each, corresponding to the vital epidermis
- 5 x 5 slices of 40 μm each, corresponding to 5 layers of dermis

[0039] All slices and the remaining stumps were extracted, and the amount of tacrolimus was determined by HPLC-MS. Moreover, the acceptor fluid and the fluid removed from the stratum corneum after each test were also analysed for tacrolimus. Each test was performed in triplicate, using skin from three different donors.

[0040] For comparison, a similar series of experiments using a commercial tacrolimus ointment (Protopic® 0.1 %, Astellas Pharma, 20 mg per skin sample and FRANZ cell) was conducted.

[0041] In result, it was found that the penetration of tacrolimus into the relevant skin layers was clearly superior in the case of the solution according to the invention. For example, already after 30 minutes approx. 9% of the administered dose was found in the

vital epidermis, and approx. 12% was found in the layers of the dermis (see fig. 1). For comparison, the commercial formulation delivered only about 2.5% of the dose to the vital epidermis and only about 5% to the dermis during the same period of time (see fig. 2). After 1,000 minutes, the amount in the dermis was about 30% of the dose in the case of the solution of the invention (see fig. 1), but only about 12.5% in the case of the commercial preparation (see fig. 2). At all times, the penetration depth was much higher for the composition of the invention (see fig. 3) than for the commercial product (see fig. 4).

Reference Example 2

[0042] A solution of radiolabeled D,L- α -tocopherol in F6H8 having a concentration of 10 mg/mL was prepared and used for a series of skin penetration experiments in analogy to Example 1, using excised human skin, with a few differences to the procedure of Example 1 as described below.

[0043] The amount of the formulation applied to each skin sample was 6 mg. The test period was 100 min. After the testing period, the stratum corneum of each sample was removed by the film stripping method (20 strips). Slices of the vital epidermis and the dermis were however obtained by microtomy at -40 °C.

[0044] For comparison, three pharmacopoeial ointment formulations incorporating the same concentration of D,L- α -tocopherol were prepared and tested: "Unguentum emulsificans aquosum" (DAB), "Basiscreme" (DAC), and "Lanae alcoholum unguentum aquosum" (DAB).

[0045] In result, it was surprising to find that the SFA-based formulation resulted in a much higher concentration of tocopherol in the vital epidermis than the three conventional formulations (see fig. 5).

Reference Example 3

[0046] The series of experiments of Example 2 were repeated in analogy, but using radiolabeled betamethasone-17,21-dipropionate as active ingredient at a concentration of 1 mg/mL instead of tocopherol. Another difference was that the SFA-based formulation of the drug contained 2.5 wt.-% ethanol.

[0047] Here it was found that the drug concentration in the skin layers was highest in the case of the SFA-based formulation of the invention, with a clear difference between the tested formulations with respect to the stratum corneum and the vital epidermis, but somewhat less differentiation in the dermis (see fig. 6).

Example 4

[0048] An SFA-based microemulsion with tacrolimus was prepared. Basically, 10 mg of tacrolimus were dissolved in 1.5 mg of Tween® 80 and 2 g of Brij® 30. Then 2 g of 1,2-pentandiol were added, followed by 0.3 g of F6H8 and 0.7 g of isopropyl myristate. After gentle stirring, 4 g of water were added and the mixture was homogenised until it had a transparent appearance.

REFERENCES CITED IN THE DESCRIPTION

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TOPISK FARMACEUTISK SAMMENSÆTNING BASERET PÅ SEMIFLUOREREDE ALKANER

Patentkrav

1. Topisk farmaceutisk sammensætning til anvendelse ved forebyggelse eller behandling af
5 en sygdom, der påvirker huden eller et hudvedhæng, hvilken sammensætning omfatter en effektiv mængde af en aktiv bestanddel og en semifluoreret alkan ifølge formelen
RFRH hvor RF er et ligekædet perfluoreret carbonhydridsegment med 4 til 12 carbonatomer, og RH er en ligekædet alkylgruppe med 4 til 8 carbonatomer, hvor den sygdom, der påvirker huden, er acne, og den aktive bestanddel er et antiinfektionsmiddel, som er valgt blandt
10 azithromycin, erythromycin, clindamycin og minocyclin; eller den sygdom, der påvirker huden, er psoriasis, og den aktive bestanddel er et immunundertrykkende makrolidmiddel, som er valgt blandt tacrolimus, sirolimus, everolimus, pimecrolimus, ridaforolimus, temsirolimus, zotarolimus og ciclosporin A;
og hvor sammensætningen skal administreres på huden eller et hudvedhæng.
- 15 2. Sammensætning til anvendelse ifølge krav 1, hvor den semifluorerede alkan er valgt blandt F4H5, F4H6, F4H8, F6H6 og F6H8, hvor F betegner et perfluoreret carbonhydridsegment, H betegner et ikke-fluoreret segment, og tallet er antallet af carbonatomer i det tilhørende segment.
3. Sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvilken
20 sammensætning er i form af en flydende eller halvfast opløsning, emulsion eller mikroemulsion.
4. Sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvilken sammensætning omfatter et fysiologisk acceptabelt co-opløsningsmiddel, som fortrinsvis er valgt blandt ethanol, acetone, ethylacetat, isopropylalkohol, glycerol, propylenglycol, pentylenglycol, polyethylenglycol, flydende paraffin, triglyceridolier, hydrofluorcarboner
25 såsom HFA 134a og/eller HFA 227 og flydende mono- eller diglycerider.
5. Sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor sygdommen eller lidelsen påvirker hudens vitale epidermis, dermis og/eller hypodermis.
6. Sammensætning til anvendelse ifølge et hvilket som helst foregående krav, hvor den
30 aktive bestanddel afgives til hudens vitale epidermis, dermis og/eller hypodermis.

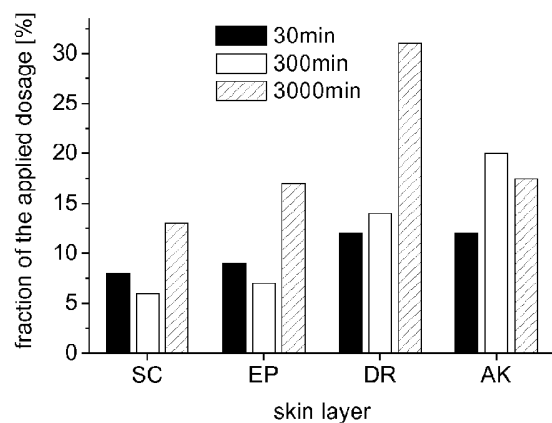
DRAWINGS

Fig. 1

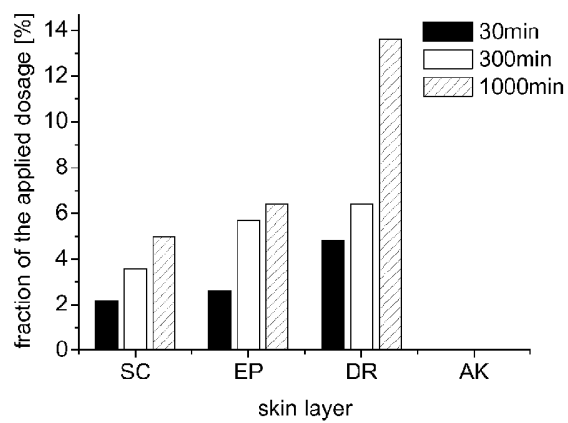


Fig. 2

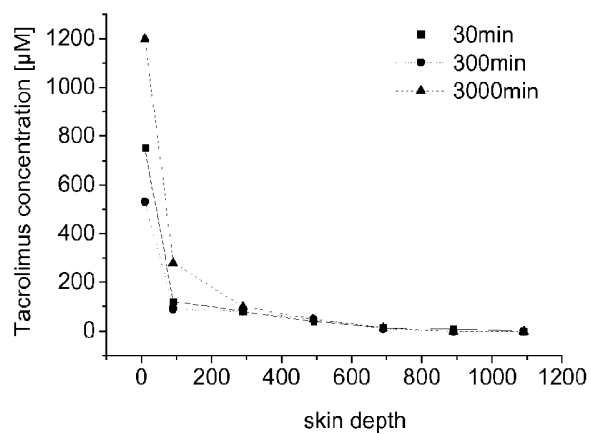


Fig. 3

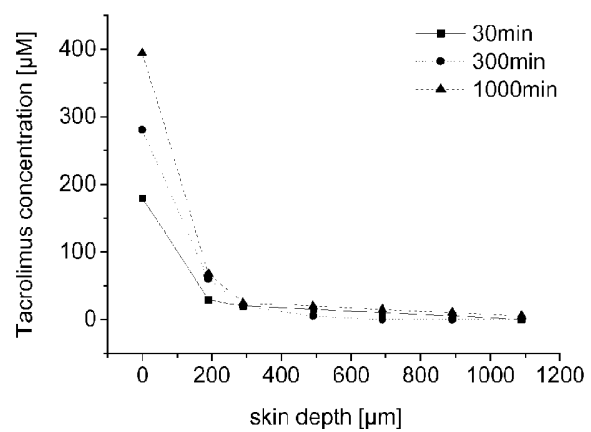


Fig. 4

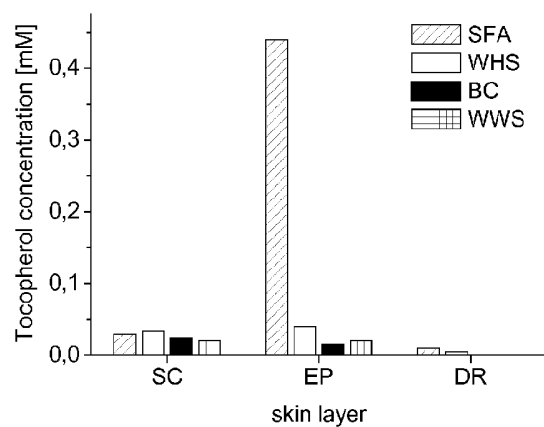


Fig. 5

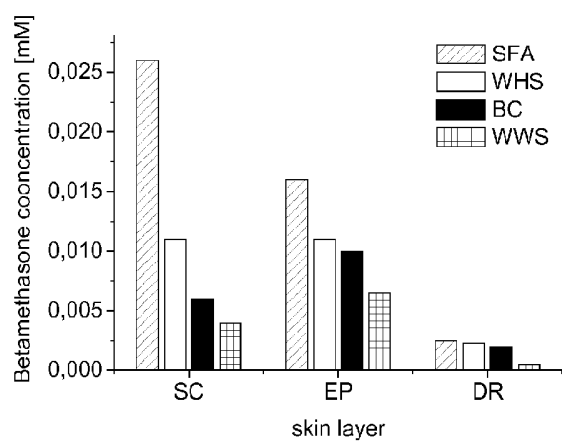


Fig. 6