

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2006 (14.12.2006)

PCT

(10) International Publication Number
WO 2006/131401 A3

(51) International Patent Classification:

A61K 9/06 (2006.01) A61K 31/59 (2006.01)
A61K 9/107 (2006.01) A61K 47/24 (2006.01)
A61K 31/57 (2006.01)

(21) International Application Number:

PCT/EP2006/005831

(22) International Filing Date: 22 May 2006 (22.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/689,282 10 June 2005 (10.06.2005) US

(71) Applicant (for all designated States except US): **GALDERMA S.A.** [CH/CH]; Zugerstrasse 8, CH-6330 Cham (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANDRES, Philippe** [FR/FR]; 126, avenue des Termes, F-06530 Peymeinade (FR). **MALLARD, Claire** [FR/FR]; Domaine La Jouvencelle, 1122 Chemins du Château, F-06250 Mougins (FR).

(74) Agent: **ANDRAL, Christophe**; L'Oréal - D.I.P.I., 25-29 Quai Aulagnier, F-92665 Asnieres-Sur-Seine Cedex (FR).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:

15 March 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2006/131401 A3

(54) Title: CONTROLLED RELEASE OF A DRUG THROUGH SKIN ON THE BASIS OF A TOPICAL COMPOSITION COMPRISING A DRUG, A FILM-FORMING SILICONE AND AT LEAST ONE VOLATILE SOLVENT

(57) Abstract: The invention concerns a method for the controlled release of a drug through skin, which method comprises topically administering a composition that comprises at least one solubilized drug, a film-forming silicone, and at least one volatile solvent.

Method of Controlled release of a drug through skin

5 The present invention pertains to the field of drug formulation for topical administration.

Background:

10 The poor penetration of drugs into the skin (and, partially, the permeation across the *Stratum corneum*) often limits the efficacy of topical formulations. Basically, skin penetration can be enhanced by the following strategies: (i) increasing drug diffusivity in the skin; (ii) increasing drug solubility in the skin, and/or (iii) increasing the degree of saturation of the drug in the formulation. However supersaturated formulations, in which the degree of saturation of the drug is increased compared to conventional formulations, are
15 often unstable, mainly because of crystallisation of the drug.

Summary of the invention:

20 The invention provides a method for the controlled release of a drug through skin, which method comprises topically administering a composition that comprises at least one solubilized drug, a film-forming silicone, and at least one volatile solvent.

More particularly the invention provides a method wherein the drug penetrates the upper layers of the skin that serves as a reservoir wherein the drug concentrates before being released to dermis.

25 For instance the drug may be vitamin D or a vitamin D analogue, such as calcitriol, or a corticosteroid, such as clobetasol or clobetasol-17-propionate, alone or in combination.

Legends to the figure:

30 The figure shows the results of a blanching test, presented as mean values of visual core across time after topical application of Dermoval®,

Daivobet®, Diprolene® creams, or a silicone ointment, as described in Example 2.

5

General description of the invention:

The inventors have found out that topical compositions that comprise at least one solubilized drug, a film-forming silicone, and at least one volatile solvent allow for the controlled release of the drug through skin, while showing a good stability. The release of the drug is slow and sustained, which makes it possible to lower the dosage. The drug can thus be administered at a dosage that is lower than the dosage used for compositions comprising the same drug, but free of the film-forming silicone and the volatile solvent.

The drug penetrates into the skin according to a specific zero-order kinetic, which means that the drug concentration exhibits a linear variation vs time, and that the penetration is constant and sustained. The drug is first maintained within the upper layers of the skin, that is to say the layers consisting of :

- *Stratum corneum*,
- *Stratum lucidum*,
- *Stratum granulosum*, and
- *Stratum germinativum* (including *Stratum spinosum* and *Stratum basale*).

The release of the drug into the lower layers (i.e. dermis and hypodermis) is controlled by the *in situ* supersaturation of the drug. Supersaturation is achieved when the solvent evaporates after the composition is applied onto skin. This evaporation concentrates the drug in solution, which favors its penetration in the upper layers of the skin and creates a reservoir effect. In parallel, the silicone allows the control of the evaporation kinetic of the solvent and the control of the crystallisation of the drug, which also favors its penetration.

The composition described herein comprises at least one drug, i.e. a pharmaceutically active ingredient. In particular it may comprise two drugs.

Examples of drugs of interest are vitamin D or a vitamin D analogue.

The term "vitamin D" means the various forms of vitamin D such as vitamin D₁, D₂, D₃ or vitamin D₄.

The term "vitamin D analogue" means the compounds that exhibit
5 analogous biological properties compared to vitamin D, in particular with regard to the transactivation of the response elements of vitamin D (VDRE), such as an agonist or antagonist activity towards the vitamin D receptors. These compounds preferably are synthetic compounds that comprise the skeleton of
10 vitamin D with modifications of lateral chains and/or that also comprise modifications within this skeleton. The analogues may comprise structural analogues, in particular biaromatic compounds.

Preferably the vitamin D analogue is selected from the group consisting of calcitriol, calcipotriol, doxercalciferol, secalcitol, maxacalcitol, seocalcitol, tacalcitol, paricalcitol, falecalcitriole, 1 α ,24S-dihydroxy-vitamine D₂, 1(S),3(R)-
15 dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-séco-pregna-(Z),7(E),10(19)-triene and mixture thereof. Most preferably, it is calcitriol.

Further examples of vitamin D analogues include those described in documents WO 02/34235, WO 00/64450, EP1124779, EP1235824,
20 EP1235777, WO 02/94754, WO 03/050067 et WO 00/26167. The compounds described in WO 00/26167 relate to structural analogues of vitamin D that show a selective activity on cell proliferation and differentiation without showing hypercalcemic activity.

Advantageously, the quantity of vitamin D or vitamin D analogue
25 solubilized in the composition is from 0.00001 to 5 % w/w, preferably from 0.0001 to 3 % w/w and more preferably from 0.0003 to 1 % w/w.

Another drug of interest, alone or in combination with vitamin D or the vitamin D analogue, is a corticosteroid.

The term "corticosteroid" means a topical steroid of group I, II, III or IV
30 (strong or weak).

More particularly, it may be selected from the group consisting of betamethasone, clobetasol, clobetasone, desoximethasone, diflucortolon,

diflorasone, fluocinonide, flumethasone, fluocinolol, fluticasone, fluprednidene, halcinonide, hydrocortisone, mometasone, triamcinolon, pharmaceutically acceptable esters or acetonides thereof, and mixtures thereof.

Examples of esters or acetonides include 17-valerate, 17-propionate,
5 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl- β -alaninate, acetonide-21-(3,3-dimethylbutyrate) and 17-butyrate.

Most preferably, the corticosteroid is clobetasol or clobetasol-17-propionate.

Advantageously, the quantity of corticosteroid in a solubilized form in
10 the composition is from 0.0001 to 1 % w/w, more preferably from 0.0005 to 3 % w/w, and more preferably from 0.001 to 0.1 % w/w.

In a preferred embodiment, the active ingredients are solubilized in the same solvent or in several solvents.

The solvent is selected among pharmaceutically acceptable
15 compounds, i.e. compounds that are suitable for a topical application.

Preferred volatile solvents include alkanols, alkylglycols, alkylketones and/or alkyl esters wherein the alkyl moieties contain from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, such as ethanol, isopropanol, n-butanol, ethyl acetate, acetone, and mixtures thereof.

20 Preferably the volatile solvent is ethanol, especially when the drugs are calcitriol and clobetasol-17-propionate.

Advantageously, the quantity of solvent within a composition is from 1 to 50 % w/w (based on the total weight of the composition), preferably from 2 to 40 % w/w and more preferably from 5 to 20 % w/w.

25

The film-forming silicone used in the invention preferably comprises at least one polyorganosiloxane elastomer.

The term "polyorganosiloxane elastomer" hereby refers to any siloxane polymer, which is chemically cross-linked and which exhibits viscoelastic
30 properties.

Examples of suitable polyorganosiloxane elastomers according to the invention are those described in patents US 4,980,167 and US 4,742,142. The

used polyorganosiloxanes may especially be addition products (adducts) resulting from hydrosylation, and/or polymeric products deriving from the addition of (i) a polyorganosiloxane having unsaturated groups, such as vinyl or allyl groups, for example linked to at least an atom, and (ii) another silicone product able to be involved in the addition reaction, such as an organohydrogenopolysiloxane.

According to a specific embodiment, the polyorganosiloxane elastomer is present in a least one volatile silicone oil that is a linear or cyclic polyorganosiloxane oil having 2 to 10 silicon atoms.

The terms "polyorganosiloxane oils" hereby refers to any silicone oil able to evaporate in contact of skin, mucosa or keratinic fibers preferably with an evaporation duration of less than 1 hour, at ambient temperature and water atmospheric pressure.

Polyorganosiloxane oils useful in the invention are, for example, linear or cyclic polyorganosiloxanes having 2 to 10 silicon atoms, optionally comprising alkyl or alkoxy groups having 1 to 22 carbon atoms. Silicone oils used in the invention advantageously exhibit a viscosity of at most $6 \cdot 10^{-6} \text{ m}^2/\text{s}$ (6 centistokes).

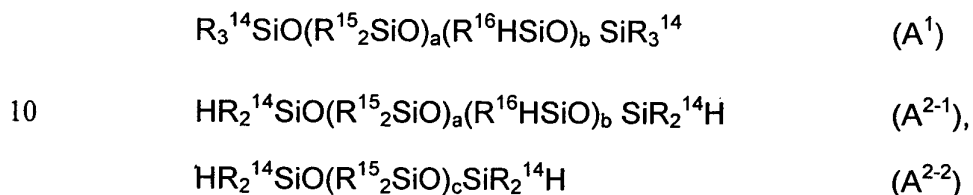
Suitable volatile silicone oils especially include cyclomethicones and/or dimethicones of low molecular weight. In this scope, cyclic polyorganosiloxanes, especially cyclic methoxylated organopolysiloxane, with a 4-membered to 12-membered siloxane ring such as octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane, may be used. Other suitable volatile silicone oils are dodecamethylcyclohexasiloxane, heptamethylhexyltrisiloxane, heptamethyloctyltrisiloxane, hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, and mixtures thereof.

A particularly suitable film-forming silicone according to the invention comprises a polyorganosiloxane elastomer in decamethyltetrasiloxane. In this scope, a preferred silicone product is the so-called "ST Elastomer 10[®]" of DOW CORNING, which is formulated in the form of a viscous and translucent gel.

According to a specific embodiment, the film-forming silicone used in the method of the invention is a silicone product obtained by a cross-linking of :

- (A) a polysiloxane having $\equiv\text{SiH}$ groups ;
 - (B) an alpha, omega-diene ;
 - 5 (C) a polysiloxane having a low molecular weight,
- in the presence of a catalyst.

In this scope, polysiloxane (A) advantageously comprises one or more compounds having one of the following formulae (A¹), (A²⁻¹) and (A²⁻²) :



wherein :

- R¹⁴, R¹⁵ et R¹⁶ are similar or different, and each represents an alkyl group with 1 to 6 carbon atoms ;
- 15 - a is an integer having a value of 0 to 250,
- b is an integer having a value of 1 to 250 ; and
- c is an integer having a value of 0 to 250.
- Preferably, polysiloxane (A) contains compounds of above formulae (A²⁻¹) and/or (A²⁻²), preferably together with compounds of formula (A¹), , with a molar ratio (A²⁻¹ + A²⁻²) : (A¹) preferably between 0 to 20, especially from 0 to 5.
- 20

Alpha, omega - diene (B) is a compound of formula $\text{CH}_2=\text{CH}(\text{CH}_2)_d\text{CH}=\text{CH}_2$, wherein d is an integer having a value of 1 to 20.

Representative examples of suitable alpha, omega - diene are especially 1,4-pentadiene, 1,5-hexadiene, 1,6-heptadiene, 1,7-octadiene, 1,8-nonadiene, 1,9-decadiene, 1,11-dodécadiene, 1,13-tetradecadiene, et 1,19-eicosadiene.

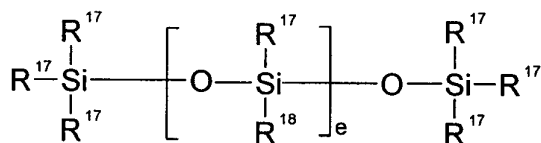
Polysiloxane (C) may especially include, alone or in combination :

(C1) linear, branched, or cyclic volatile methylsiloxanes, for example :

- volatile methoxysiloxanes selected from hexamethyldisiloxane, octamethyltrisiloxane, décamethyltetrasiloxane, dodecamethylpentasiloxane, tetradecamethylhexasiloxane, and/or hexadecamethylheptasiloxane ;
- 5 - cyclic volatiles methylsiloxanes such as hexamethylcyclotrisiloxane, octamethylcyclotetrasiloxane, decamethylcyclopentasiloxane, and/or dodecamethylcyclohexasiloxane.
- branched volatile methylsiloxanes, such as heptamethyl-3-[(trimethylsilyl)oxy]-trisiloxane, hexamethyl-3,3,bis[(trimethylsilyl)oxy]-trisiloxane, and/or pentamethyl[(trimethylsilyl)oxy]-cyclotrisiloxane ;

(C2) alkyl- and/or aryl- siloxanes, which are linear, or cyclic, and which are volatile or non-volatile,

especially low molecular weight, non-volatile, compounds having a viscosity of about 100 to 1000 mm²/s (centistokes), especially those depicted by the following formula :



wherein :

- e has a value preferably of 80 to 375,
- 20 - R¹⁷ et R¹⁸ are alkyl radical having 1 to 20 carbon atoms, or an aryl group such as a phenyle,

for example polydimethylsiloxanes, polydiethylsiloxanes, polymethyl-ethylsiloxanes, polymethylphenylsiloxanes and/or polydiphenylsiloxanes ;

(C3) functionalized siloxanes, which are linear, or cyclic, especially fluid siloxanes, for example functionalized with groups selected from acrylamides, acrylates, amides, amino, carbinol, carboxy, chloroalkyles, epoxy, glycol, cetal, mercapto, methylester, perfluoro and silanol.

Preferably, Polysiloxane (C) is a low molecular weight silicone oil selected from volatile methylsiloxanes, of low molecular weight, which are linear or cyclic.

5 Other polysiloxanes suitable for an use as film-forming silicones according to the invention are silicone polymers with an average molecular weight of at least 10 000 (e.g. from 10 000 to 10 000 000). Examples of such polysiloxanes include copolymers of crosslinked siloxanes, especially copolymers of dimethicone or dimethicone derivatives, for example siloxane
10 stearyl methyl-dimethyl copolymers (such as « Gransil SR-CYC[®] » of Grant Industries), copolymers of the type of the « Polysilicone-11[®] » (crosslinked elastomer silicone formed by reaction of a vinyl-terminated silicone with methylhydrodimethylsiloxane in the presence de cyclomethicone), crosslinked
15 cetearyl dimethicone/vinyl dimethicone copolymers (namely copolymers of cetearyl dimethicone crosslinked with a vinyl dimethyl polysiloxane), crosslinked dimethicone/phenyl vinyl dimethicone copolymers (namely dimethylpolysiloxane copolymers crosslinked with phenyl vinyl dimethylsiloxane), and crosslinked
20 dimethicone/vinyl dimethicone copolymers (namely dimethylpolysiloxane copolymers crooslinked with vinyl dimethylsiloxane).

20 Silicones formulated as a gel may be obtained especially from the Grant Industries. Examples of such gels especially include :

- mixtures of cyclomethicone and polysilicone-11, such as commercial product « Gransil GCM5[®] »,

25 - mixtures of cyclotetrasiloxane and polysilicone-11, such as commercial product « Gransil PS-4[®] »,

- mixtures of cyclopentasiloxane and polysilicone-11 such as commercial product « Gransil PS-5[®] »,

- mixtures of cyclopentasiloxane, dimethicone and polysilicone-11, such as commercial product « Gransil DMCM-5[®] »,

- mixtures of cyclotetrasiloxane, dimethicone and polysilicone-11, such as commercial product « Gransil DMCM-4[®] »,

- mixtures of polysilicone-11 and isododecane such as commercial product « Gransil IDS[®] », and

5 - mixtures of cyclomethicone, polysilicone-11 and phytosphingosine, such as commercial product « Gransil SPH[®] ».

Other examples are gels of crosslinked polymers of cyclopentasiloxane and dimethicone/vinyl dimethicone, such as « SFE839[®] » of the General Electric Company. Yet other silicone gels are those commercialized by the Shin-Etsu
10 Company under references KSG-15, KSG-16 and KSG-17.

According to a specific embodiment, the composition used in the method of the invention is advantageously free from polyorganosiloxane having alkyl groups.

15

Whatever its exact nature, the film-forming silicone of the method of the invention is advantageously present in the composition at a concentration of 20 to 90% weight based on the total weight of the composition, preferably of between 30 and 80%.

20 The compositions described herein may further contain an oily additive, such as isopropyl palmitate, dicaprilic ether, dimethicone, or mixtures thereof.

The compositions described herein may also contain flavour-enhancing agents, preservatives such as para-hydroxybenzoic acid esters, stabilizing agents, moisture regulators, pH regulators, osmotic pressure modifiers,
25 emulsifying agents, UV-A and UV-B screening agents, and antioxidants such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene, superoxide dismutase, ubiquinol, or certain chelating agents.

Preferably, the composition is in form of a cream, a gel, an ointment or a pomade.

Preferably, the composition is substantially free of water, i.e. it contains less than 5 % w/w of water, preferably less than 3 %, most preferably 0 % of water.

Preferred compositions comprise :

- 5
- isopropyl palmitate
 - cyclopentasiloxane
 - cyclomethicone 5/dimethicone crosspolymer
 - calcitriol
 - clobetasol-17- proprionate

10

 - ethanol.

In a preferred embodiment, the composition comprises :

- isopropyl palmitate 0.5-2%
- cyclopentasiloxane 10-20%
- cyclomethicone 5/dimethicone crosspolymer 70-80%

15

- calcitriol 0.0001-0.0005%
- clobetasol-17-proprionate 0.01-0.05%
- ethanol 5-10%.

Examples:

20

Example 1: Preparation of a controlled-release formulation

The process described below is a general manufacture process of a silicone ointment that comprises a vitamin D analogue and a corticosteroid. The process is performed at room temperature, between 20°C and 25°C.

25 *First step* : preparation of the phase that comprises the silicone (phase I) :

The ingredients of phase I ("Elastomer ST 10®", silicone oil and oily additive) are weighed in a vessel. The mixture is homogenised until obtention of a homogenous gel.

30 *Second step* : preparation of the phase that comprises the active ingredients (phase II) :

A parent solution is prepared, that comprises a vitamin D analogue in an appropriate solvent, and an anti-oxidant. The solution is stirred until solubilization of the active ingredient.

The corticosteroid is weighed and put in the solvent. The solution is stirred until solubilization of the active ingredient.

The two active phases are incorporated in phase I under stirring. The mixture is homogenised.

When the solvent is the same for the two active ingredients, the corticosteroid is added to the parent solution of vitamin D analogue.

Table 1 :

Composition	
Ingredients	Quantities in % (w/w)
PHASE I : ISOPROPYL PALMITATE ¹ (oily additive)	1
CYCLOPENTASILOXANE ² (solvent)	16
CYCLOMETHICONE 5 / DIMETHICONE CROSSPOLYMER (silicone agent ³)	74.95
PHASE II : BUTYLHYDROXYTOLUENE (anti-oxidant)	0.04
CALCITRIOL (active ingredient)	0.0003
CLOBETASOL PROPIONATE (active ingredient)	0.025
ABSOLUTE ETHANOL (solvent)	8

¹ Crodamol IPP®

² Mirasil CM5®

³ Elastomer ST 10®

Example 2: Sustained-release of the drug

The objective of this study was to compare a fixed-combination of calcitriol 3 µg/g and clobetasol propionate 250 µg/g (composition of example 1)

by evaluation of its blanching capacity to three marketed corticosteroids formulations:

- Dermoval[®] (Temovate[®]) cream (clobetasol propionate 500µg/g)
- Diprolene[®] cream (betamethasone dipropionate 500µg/g)
- 5 - Daivobet[®] ointment (fixed-combination containing calcipotriol 50 µg/g and betamethasone dipropionate 500 µg/g).

The creams of reference (Dermoval[®], Diprolene[®], Daivobet[®]) above do not contain a combination of silicone and volatile solvent.

10 ***Methodology :***

This study was conducted as a single center, investigator masked, active controlled, intra-individual comparison.

The tested products were randomly allocated to pre-marked 2.2 cm diameter sites on forearms. Applications were performed by a trained research assistant out of the sight of the blanching evaluators. The study products were
15 administrated as six hours non occlusive application.

Visual and chromametric evaluations of vasoconstriction were made within 30 minutes before product application, and 10 minutes, 2 hours, 4 hours, 6 hours, 18 hours and 22 hours after removal of the excess (removal took place
20 6 hours after study products application). Assessment of blanching visual scores (primary pharmacodynamics variable) was performed by two independent trained evaluators, using a 5-point scale (0: no blanching to 4: maximal blanching). Chromametric evaluation (secondary pharmacodynamics variable) was based on chromametric parameters (a* and L* value), using a
25 ChromaMeter Minolta CR 300.

Safety assessment was conducted for all subjects at every visit after enrolment in the study. The primary parameter for the safety measurement was the record of adverse events.

Visual scoring was to be made independently by two experienced
30 evaluators using the following 5 point-scale:

- 0 No change in skin color
- 1 Slight (barely visible) blanching

- 2 Obvious blanching
- 3 Intense blanching
- 4 Maximal blanching considered being

For visual scores, the analyzed variable was the mean of the two
 5 evaluators' scores on each site. The area under the curve was calculated by
 subject and by treatment from T0 (before application) up to T28h (22 hours after
 product removal). The chromametric variables a^* and L^* were adjusted
 according to their baseline value before application: $-\Delta a^*$ and ΔL^* . The area
 under the curve was calculated by subject and by treatment from T0 (before
 10 application up to T28h (22 hours after product removal). The areas under the
 curve were submitted, by parameter, to analyses of variance including subject,
 zone and treatment as factors in the model.

The treatments were compared and classified using a Tukey multiple
 comparison test, which was performed at the 5% two sided significance level.

15

Results:

Twenty-four (2 male and 22 female healthy subjects aged 20.4 to 42.3
 years) were enrolled in the study. Twenty-four subjects completed the study
 according to the protocol. None of them was excluded from the analysis.

20 Regarding the evaluation of the blanching visual scores (based on a 5-
 point scale), the analyzed variable was the area under the curve (AUC) of mean
 of the two evaluators' scores on each site. This AUC was calculated by subject
 and by treatment from T0 (before application) up to T28h (22 hours after
 product removal). These data are summarized in Table 2 below :

25

		Daivobet [®]	Dermoval [®]	Diprolene [®]	silicone ointment
AUC	n	24	24	24	24
	Mean	29.69	55.46	26.40	26.75
	± SEM	± 2.76	± 2.66	± 2.73	± 2.47
	Median	30.84	58.51	25.54	27.93

(Min,	(0.48,	(32.25,	(6.23,	(6.00,
Max)	53.06)	76.25)	48.79)	56.88)

Based on the visual scores of blanching (primary pharmacodynamics variable), investigational products were classified in two separate groups with a significantly different vasoconstriction activity, as follows:

- 5 - Dermoval[®] cream >
 - silicone ointment, Daivobet[®] ointment, Diprolene[®] cream.

However a very specific vasoconstriction profile was observed with the silicone ointment demonstrating a very slow release. The maximal effect was not reached after T0 + 22 hours, that is 28 hours after product application. The AUC
 10 of this product is therefore not complete and cannot be appropriately compared to the other products for which entire AUC could be calculated.

The chromametric parameters L* and a* supported the results obtained from visual scores.

In terms of safety analysis, neither treatment-related adverse events
 15 nor serious adverse events were reported. Only one unrelated adverse event (common cold) was reported during the study. All tested products were therefore considered well-tolerated.

Conclusion :

20 The release of clobetasol from the silicone ointment is continuously increasing with the maximal effect of vasoconstriction not reached after 28 hours.

25 **Example 3 : Distribution of the drug :**

[Example to be completed with greater details on the protocol and the interpretation of results]

Clobetasol-17-propionate was shown to accumulate in the *Stratum corneum* 16 hours after application on a human skin (Franz' cells).

Table 3 :

Formulations	% Applied Dose				
	Stratum corneum / Epidermis	Dermis	Absorbed dose	Dermal delivery	Mass balance
Temovate® Cream	5.33 ± 0.54	2.62 ± 0.38	0.48 ± 0.01	8.43 ± 0.79	98.76 ± 2.33
Silicone Ointment	8.24 ± 1.28	1.12 ± 0.18	0.59 ± 0.01	9.96 ± 1.36	97.82 ± 3.66

CLAIMS

1. A method for the controlled release of a drug through skin, which
5 method comprises topically administering a composition that comprises at least
one solubilized drug, a film-forming silicone, and at least one volatile solvent.
2. The method of claim 1, wherein the drug is administered at a
dosage that is lower than the dosage used for compositions comprising the
10 same drug, but free of the film-forming silicone and the volatile solvent.
3. The method of claim 1, wherein the composition comprises two
drugs.
- 15 4. The method of claim 1, wherein the composition comprises
solubilized vitamin D or a vitamin D analogue.
5. The method of claim 4, wherein the vitamin D analogue is selected
from the group consisting of calcitriol, calcipotriol, doxercalciferol, secalcitol,
20 maxacalcitol, seocalcitol, tacalcitol, paricalcitol, falecalcitriole, $1\alpha,24S$ -
dihydroxy-vitamine D₂, 1(S),3(R)-dihydroxy-20(R)-[[(3-(2-hydroxy-2-propyl)-
phenyl)-methoxy)-methyl]-9,10-séco-pregna-(Z),7(E),10(19)-triene and mixture
thereof.
- 25 6. The method of claim 5, wherein the vitamin D analogue is
calcitriol.
7. The method of claim 1, wherein the composition comprises a
solubilized corticosteroid.
- 30 8. The method of claim 7, wherein the corticosteroid is selected from
the group consisting of betamethasone, clobetasol, clobetasone,
desoximethasone, diflucortolon, diflorasone, fluocinonide, flumethasone,

fluocinolon; fluticasone, fluprednidene, halcinonide, hydrocortisone, mometasone, triamcinolon, pharmaceutically acceptable esters or acetonides thereof, and mixtures thereof.

5 9. The method of claim 7, wherein the esters or acetonides are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl- β -alaninate, acetonide-21-(3,3-dimethylbutyrate) and 17-butyrate.

10 10. The method of claim 7, wherein the corticosteroid is clobetasol-17-propionate.

15 11. The method of claim 1, wherein the volatile solvent is selected from the group consisting of alkanols, alkylglycols, alkylketones and/or alkyl esters wherein the alkyl moieties contain from 1 to 6 carbon atoms.

12. The method of claim 11, wherein the volatile solvent is ethanol.

20 13. The method of claim 1, wherein the film-forming silicone comprises at least one polyorganosiloxane elastomer.

25 14. The method of claim 13, wherein the polyorganosiloxane elastomer is present in a least one volatile silicone oil that is a linear or cyclic polyorganosiloxane oil having 2 to 10 silicium atoms.

15. The method of claim 1, wherein the silicone is at a concentration of 20 to 90% weight based on the total weight of the composition.

30 16. The method of claim 1, wherein the solvent is at a concentration of 1 to 50% weight based on the total weight of the composition.

17. The method of claim 1, wherein the composition is in form of a cream, a gel or an ointment.

18. The method of claim 1, wherein the composition is substantially
5 free of water.

19. The method of claim 1, wherein the composition comprises :

- isopropyl palmitate
- cyclopentasiloxane
- 10 -cyclomethicone 5/dimethicone crosspolymer
- calcitriol
- clobetasol-17- proprionate
- ethanol.

15 20. The method of claim 19, wherein the composition comprises, in weight/weight of the composition:

- isopropyl palmitate 0.5-2%
- cyclopentasiloxane 10-20%
- cyclomethicone 5/dimethicone crosspolymer 70-80%
- 20 -calcitriol 0.0001-0.0005%
- clobetasol-17-proprionate 0.01-0.05%
- ethanol 5-10%.

21. Method of administering to a host a composition according to claims 1 to
20.

25

22. Method of treating skin disorders using a composition according to claims 1 to 20.

23. Method of treatment according to claim 22, wherein the skin disorder is
30 psoriasis.