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⑤④ STEROID LOTION.

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EP-A- 0 057 401
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Chemical Abstracts, vol. 106, no. 5, 2 February 1987, (Columbus, Ohio, US), Nakamura, Masuhisa et al.: "Local anti-inflammatory and systemic effect of alclometasone dipropionate", see page 90, abstract no. 44213h

⑦③ Proprietor: **SCHERING CORPORATION**
2000 Galloping Hill Road
Kenilworth New Jersey 07033 (US)

⑦② Inventor: **SEQUEIRA, Joel, A.**
18 Stuyvesant Oval
New York, NY 10009 (US)
 Inventor: **MUNAYYER, Farah, J.**
494 Passaic Avenue
West Caldwell, NJ 07006 (US)
 Inventor: **GALEOS, Rebecca**
18 Clinton Street
Bloomfield, NJ 07003 (US)

⑦④ Representative: **von Kreisler, Alek et al**
Patentanwälte von Kreisler Seiting Werner
Deichmannhaus am Hauptbahnhof
W-5000 Köln 1 (DE)

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Description

This invention relates to a topical lotion for use in the application of steroid medicaments. More particularly, this invention relates to an improved lotion vehicle for steroids having improved properties.

EP-A-0 129 283 discloses topical pharmaceutical compositions containing a corticosteroid as the active ingredient and a penetration-enhancing vehicle. It is directed to a specific vehicle comprising a C₃-C₄ diol and a cell-envelope disordering compound. Propylene glycol is mentioned as one of the C₃-C₄ diol compounds that can be employed in combination with the cell-envelope disordering compound. Optional ingredients in this prior art composition include, inter alia, a solvent, such as water or isopropanol and a thickening agent. The cell-envelope disordering compounds disclosed in the reference are methyl laurate, oleic acid, oleyl alcohol, monoolein, myristyl alcohol and mixtures thereof.

The present invention provides a corticosteroid lotion formulation exhibiting high vasoconstrictor activity and excellent anti-inflammatory activity in steroid responsive dermatoses. The addition of propylene glycol to a hydro-alcoholic lotion base exhibits significantly higher vasoconstrictor activity than the corresponding lotion without propylene glycol. This increase in vasoconstrictor activity appears to be unique to propylene glycol since substitution of propylene glycol with another glycol, such as hexylene glycol or polyethylene glycol 400, decreases the vasoconstrictor activity of the lotion formulation.

This present invention comprises a topical composition for the treatment of dermatological disorders that are responsive to corticosteroids. The topical composition comprises an amount effective to treat an inflammation of a dermatologically acceptable anti-inflammatory corticosteroid in a hydro-alcoholic base comprising:

- (a) 15 to 50 % by weight propylene glycol
- (b) 20 to 40 % by weight isopropyl alcohol
- (c) 20 to 80 % by weight water
- (d) 0.1 to 0.5 % by weight of a thickening agent
- (e) sufficient buffer to adjust the pH to between 3.0 to 6.0.

This invention particularly relates to topical lotions which contain a steroid anti-inflammatory agent as the active ingredient. The anti-inflammatory agents disclosed herein are of value in the topical treatment of dermatological disorders conditions responsive to anti-inflammatory drugs. Included in this category are disorders such as psoriasis, seborrheic dermatitis, atopic dermatitis, contact dermatitis and eczema.

Treatment with the lotions of this invention is usually accomplished by applying the lotion to completely cover the affected area. The usual frequency of application is two to three times daily, although adequate maintenance therapy for some patients may be with less frequent application.

The lotion of the present invention comprises a therapeutically effective amount of dermatologically acceptable anti-inflammatory corticosteroid. The therapeutically effective amount of corticosteroid is generally an amount of from 0.01 to 1.0 % by weight of the total composition. Ranges of 0.02 to 0.2 % are particularly suitable with a range of 0.05 to 0.1 % by weight being most preferable.

The particular steroid medicaments useful in the composition of the present invention are dermatologically acceptable anti-inflammatory corticosteroids. Examples of corticosteroids are betamethasone 17,21-dipropionate, alclometasone dipropionate, mometasone furoate [9 α ,21-dichloro-16 α -methyl-1,4-pregnadiene-11 β ,17 α -diol-3,20-dione-17-(2-furoate)], fluocinonide, halcinonide and desoximetasone.

This lotion composition of the present invention may contain a thickening agent to achieve a lotion consistency. Examples of thickening agents useful in the invention are: Carbomer 940[®], an acrylic acid polymer having an approximate molecular weight of 4,000,000 and available from B.F. Goodrich Chemical Company; Klucel[®], hydroxypropyl cellulose which is a propylene glycol ether of cellulose available from Hercules Inc., Methocel A[®], methyl cellulose which is a methyl ether of cellulose available from Dow Chemicals; and Polyquaternium-10[®] which is a polymeric quaternary ammonium salt of hydroxyethyl cellulose reacted with a trimethyl ammonium substituted epoxide, available from Amerchol Corporation. Cosmetic preference or stability considerations will dictate selection of the thickening agent.

The pH of the lotion composition of the present invention is in the range of 3.0 to 6.0 and preferably pH 4 to 5. Sufficient buffer solution is added to the lotion composition to maintain the pH in the desired range. Examples of buffers useful in the present invention are phosphate buffer, citrate buffer, citrate-phosphate buffer.

The lotion of the present invention is manufactured in a conventional manner by thoroughly mixing the ingredients at ambient or elevated temperatures in order to achieve solubility of ingredients where appropriate.

The following formulation example illustrate the lotion compositions of the invention. It will be apparent to those skilled in the art that many modifications thereof may be practical without departing from the purpose and intent of this disclosure. The definition of components whose chemical composition is not immediately clear from the name used may be found in the CTFA Cosmetic Ingredients Dictionary, 3rd Edition, published by Cosmetic Toiletory and Fragrance Association, Inc., Washington, D.C.

EXAMPLE 1

A 0.05% betamethasone dipropionate topical lotion formulation in accordance with the present invention having the following composition:

<u>Ingredients</u>	<u>mg/g</u>
Betamethasone 17,21-Dipropionate USP	0.64*
Sodium Phosphate Monobasic Monohydrate R	2.00
Phosphoric Acid NF -	**
Sodium Hydroxide R	**
Propylene Glycol USP	300.00
Isopropyl Alcohol USP	300.00
Hydroxypropyl Cellulose NF	1.50
Purified Water USP q.s.	1.00 g

* Equivalent to 0.5 mg Betamethasone/g

** Used to adjust the pH to 4.5 ± 0.2

In preparing the topical lotion formulation, the steroid is dissolved in isopropyl alcohol. Hydroxypropylcellulose is dispersed in the alcoholic solution. A solution of sodium phosphate monobasic in water is added to the isopropyl alcoholic solution. Propylene glycol is then added and the solution is adjusted to total weight. Phosphoric acid is used to adjust the lotion to the target pH. In case the thickening agent is Carbomer 940®, sodium hydroxide is added to neutralize the acidic pH of the lotion and to achieve a final pH of approximately 4.5.

EXAMPLE 2

A 0.05% alclometasone dipropionate lotion formulation in accordance with the present invention having the following composition.

Ingredientsmg/g

Alclometasone dipropionate

0.5

Carbomer 940 ^(R)

2.60

Sodium Hydroxide, R

0.04

Propylene Glycol, USP

200.0

Isopropyl Alcohol, NF

300.0

Hydrochloric Acid

*

Purified Water, USP q.s. ad to

1.0 g

* Used to adjust the pH to 4.5

EXAMPLE 3

A 0.1% mometasone furoate lotion formulation in accordance with the present invention having the following composition:

Ingredientsmg/g

Mometasone furoate

1.0

Alcohol Isopropyl USP

400.0

Propylene Glycol USP

300.0

Hydroxypropylcellulose (Klucel HF)

1.5

Sodium Phosphate Monobasic Monohydrate R

2.0

Phosphoric Acid NF

*

Water Purified USP q.s. to make

1 g

* Used to adjust the pH to 4.5 ± 0.1 .Example 4

A 0.05% fluocinonide lotion formulation in accordance with the present invention having the following composition:

<u>Ingredients</u>	<u>mg/g</u>
Fluocinonide	0.50
Sodium Phosphate Monobasic Monohydrate R	2.00
Phosphoric Acid NF	*
Sodium Hydroxide R	*
Propylene Glycol USP	300.00
Isopropyl Alcohol USP	300.00
Hydroxypropyl Cellulose NF	2.00
Purified Water USP q.s.	1.00 g
* Used to adjust the pH to 4.5	

Example 5

A 0.1% halcinonide lotion formulation in accordance with the present invention having the following composition:

<u>Ingredients</u>	<u>mg/g</u>
Halcinonide	1.00
Sodium Phosphate Monobasic Monohydrate R	2.00
Phosphoric Acid NF	*
Sodium Hydroxide R	*
Propylene Glycol USP	300.00
Isopropyl Alcohol USP	300.00
Hydroxypropyl Cellulose NF	3.00
Purified Water USP q.s.	1.00 g
* Used to adjust the pH to 4.5	

Example 6

A 0.05% desoximetasone lotion formulation in accordance with the present invention having the following composition:

<u>Ingredient</u>	<u>mg/g</u>
Desoximetasone	0.50
Sodium Phosphate Monobasic Monohydrate R	2.00
Phosphoric Acid NF	*
Sodium Hydroxide R	*
Propylene Glycol USP	300.00
Isopropyl Alcohol USP	300.00
Hydroxypropyl Cellulose NF	4.00
Purified Water USP	q.s. 1.00 g

* Used to adjust the pH to 4.5

Local anti-inflammatory activity of the topical compositions of this invention were tested by the vasoconstrictor assay described by McKenzie and Stoughton, Arch. Dermatol., 88, 608 (1962).

Sixteen to 32 subjects from a pool of healthy volunteers who met certain selection criteria were selected for each study. No individual was used more frequently than once every two weeks.

Four sites, each approximately 2 cm in diameter and at least 1 cm apart, were delineated on the flexor surface of each of the subject's forearms, giving a total number of eight sites per subject. Ten (10) mg of each of the formulations tested per study were randomly applied to these sites using a Latin square design code, so that each site location received each test preparation an equal number of times.

The four sites on each arm were then covered with a protective plastic shield. Six and one half hours later the shields were removed, and the test sites were washed with soap and water. Approximately 1/2 and 18 hours after removal of the shields, (7 and 24 hours after initial application of the test materials), the sites were examined and the degree of blanching (vasoconstriction) was graded as follows: No blanching - 0; mild blanching - 1; moderate blanching - 2 and strong blanching - 3.

Table I reports the results of a topical composition of this invention containing propylene glycol with a corresponding formulation without propylene glycol. In two test panels of 24-32 subjects per panel, the lotion with propylene glycol exhibits significantly higher vasoconstrictor activity than the lotion without propylene glycol.

TABLE I

VASOCONSTRICTOR ACTIVITY OF BETAMETHASONE DIPROPIONATE
(BDP) LOTIONS

<u>LOTION</u>	<u>VASOCONSTRICTOR SCORE AT 7 HOURS</u>	
	<u>TEST 1</u>	<u>TEST 2</u>
BDP Lotion, 0.05% <u>with</u> propylene glycol	1.8	1.5
BDP Lotion, 0.05% <u>without</u> propylene glycol	1.5	1.1

Table II reports data demonstrating that when another glycol, such as hexylene glycol or polyethylene glycol 400 (PEG 400) is replaced for propylene glycol, the vasoconstrictor activity of the propylene glycol formulation, is significantly higher than the other two glycol containing formulas.

TABLE II

<u>LOTION</u>	<u>VASOCONSTRICTOR SCORE</u>	
	<u>7 HOURS</u>	<u>24 HOURS</u>
BDP Lotion, 0.05% with propylene glycol	1.5	0.6
BDP Lotion, 0.05% with hexylene glycol	0.7	0.4
BDP Lotion, 0.05% with PEG 400	0.2	0.1

Table III reports data of a 0.05% alclometasone lotion containing propylene glycol. Substituting propylene glycol with another glycol, hexylene glycol, caused a significant decrease in vasoconstrictor activity.

TABLE III

VASOCONSTRICTOR ACTIVITY OF ALCLOMETASONE DIPROPIONATE
(AD) LOTIONS

<u>LOTION</u>	<u>VASOCONSTRICTOR ACTIVITY</u>	
	<u>7 HOURS</u>	<u>24 HOURS</u>
AD Lotion, 0.05% with 20% propylene glycol	1.1	0.16
AD Lotion, 0.05% with 20% hexylene glycol	0.41	0.09

The data presented in the foregoing tables demonstrate that propylene glycol uniquely potentiates the vasoconstrictor activity and anti-inflammatory activity of steroids when formulated in a hydro-alcoholic base of this invention.

Table IV reports data of a 0.1% Mometasone furoate lotion containing propylene glycol. Substituting propylene glycol with hexylene glycol or polyethylene glycol-400 caused a significant decrease in vasoconstrictor activity.

TABLE IV

Vasoconstrictor Activity of Mometasone Furoate (MF) Lotion

<u>Lotion</u>	<u>Vasoconstrictor Activity</u>	
	<u>7 Hours</u>	<u>24 Hours</u>
MF Lotion, 0.1% with 30% propylene glycol	1.0	0.33
MF Lotion 0.1% with 30% hexylene glycol	0.13	0.06
MF Lotion 0.1% with 30% polyethylene glycol 400	0	0.04

Claims

1. A topical lotion for the treatment of inflammation which comprises 0.01 to 1.0 % by weight of the composition of a dermatologically acceptable anti-inflammatory corticosteroid in a hydro-alcoholic base comprising:
 - 15 to 50% by weight of propylene glycol;
 - 20 to 40 % by weight of isopropyl alcohol;
 - 20 to 60 % by weight water;
 - 0.1 to 0.5 % by weight of a thickening agent, and sufficient buffer to maintain the pH of the composition within the range of 3.0 to 6.0
2. The lotion of claim 1 wherein the corticosteroid comprises 0.02 to 0.2 % by weight of the composition.
3. The lotion of claim 1 wherein the corticosteroid is betamethasone 17,21-dipropionate.
4. The lotion of claim 3 wherein the betamethasone 17,21-dipropionate is present in an amount of 0.064 % by weight.
5. The lotion of claim 4 comprising:

IngredientsConcentration
(mg/g)

5	Betamethasone 17,21-Dipropionate USP	0.64*
	Sodium Phosphate Monobasic Monohydrate R	2.00
	Phosphoric Acid NF -	**
10	Sodium Hydroxide R	**
	Propylene Glycol USP	300.00
15	Isopropyl Alcohol USP	300.00
	Hydroxypropyl Cellulose NF	1.50
	Purified Water USP q.s. ad to	1.00 g

20 * Equivalent to 0.5 mg Betamethasone/g

** Used to adjust the pH to 4.5 ± 0.2

25 6. The lotion of claim 1 wherein the corticosteroid is alclometasone dipropionate.

7. The lotion of claim 6 comprising:

IngredientsConcentration
mg/g

30	Alclometasone Dipropionate	0.5
	Carbomer 940 ^(R)	2.60
35	Sodium Hydroxide, R	0.04
	Propylene Glycol, USP	200.0
40	Isopropyl Alcohol, NF	300.0
	Hydrochloric Acid	*
45	Purified Water, USP q.s. ad to	1.0 g

Used to adjust the pH to 4.5

50 8. The lotion of claim 1 wherein the corticosteroid is mometasone furoate.

9. The lotion of claim 8 comprising :

IngredientsConcentration
mg/g

Mometasone Furoate

1.0

Isopropyl Alcohol USP

400.0

Propylene Glycol USP

300.0

Hydroxypropyl Cellulose (Klucel HF[®])

1.5

Sodium Phosphate Monobasic Monohydrate R

2.0

Phosphoric Acid NF

*

Water Purified USP

q.s. ad to

1 g

* Used to adjust the pH to 4.5 ± 0.1

10. The lotion of claim 1 wherein the thickening agent is an acrylic acid polymer.

11. The lotion of claim 1 wherein the thickening agent is hydroxypropyl cellulose.

Patentansprüche

1. Topische Lotion zur Behandlung von Entzündungen, umfassend 0,01 bis 1,0 Gew.-% der Zusammensetzung eines dermatologisch annehmbaren entzündungshemmenden Corticosteroids in wäßrig-alkoholischer Grundlage, umfassend

15 bis 50 Gew.-% Propylenglycol

20 bis 40 Gew.-% Isopropylalkohol

20 bis 60 Gew.-% Wasser;

0,1 bis 0,5 Gew.-% eines Verdickungsmittels, sowie genügend Puffer, um den pH der Zusammensetzung im Bereich von 3,0 bis 6,0 zu halten.

2. Lotion nach Anspruch 1, worin das Corticosteroid 0,02 bis 0,2 Gew.-% der Zusammensetzung umfaßt.

3. Lotion nach Anspruch 1, worin das Corticosteroid Betamethason-17,21-dipropionat ist.

4. Lotion nach Anspruch 3, worin das Betamethason-17,21-dipropionat in einer Menge von 0,064 Gew.-% vorhanden ist.

5. Lotion nach Anspruch 4, umfassend:

Bestandteile	Konzentration (mg/g)
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5

Betamethason-17,21-dipropionat, USP	0,64*
Natriumphosphat, einbasiges Monohydrat R	2,00
Phosphorsäure NF	**
10 Natriumhydroxid R	**
Propylenglycol USP	300,00
Isopropylalkohol USP	300,00
15 Hydroxypropylcellulose NF	1,50
Gereinigtes Wasser USP	auf 1,00 g

* Entsprechend 0,5 mg Betamethason/g

20

** Verwendet um den pH auf 4,5 ± 0,2 einzustellen

6. Lotion nach Anspruch 1, worin das Corticosteroid Alclometasondipropionat ist.

7. Lotion nach Anspruch 6, umfassend :

25

Bestandteile	Konzentration (mg/g)
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30

Alclometasondipropionat	0,5
Carbomer 940 (R)	2,60
Natriumhydroxid R	0,04
35 Propylenglycol USP	200,00
Isopropylalkohol USP	300,00
Salzsäure	*
40 Gereinigtes Wasser USP	auf 1,0 g

* Verwendet um den pH auf 4,5 einzustellen

45

8. Lotion nach Anspruch 1, worin das Corticosteroid Mometasonfuroat ist.

9. Lotion nach Anspruch 8, umfassend :

50

55

Bestandteile	Konzentration (mg/g)
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5	Mometasonfuroat	1,0
	Isopropylalkohol USP	400,0
	Propylenglycol USP	300,0
10	Hydroxypropylcellulose (Klucel HF ^(R))	1,5
	Natriumphosphat, einbasiges Monohydrat R	2,0
	Phosphorsäure NF	*
15	Gereinigtes Wasser USP	auf 1,0 g

* Verwendet um den pH auf $4,5 \pm 0,1$ einzustellen

- 20 10. Lotion nach Anspruch 1, worin das Verdickungsmittel ein Acrylsäure-Polymer ist.
 11. Lotion nach Anspruch 1, worin das Verdickungsmittel Hydroxypropylcellulose ist.

Revendications

25 1. Lotion topique pour le traitement d'une inflammation, qui contient 0,01 à 1,0% en poids de la composition d'un corticostéroïde anti-inflammatoire dermatologiquement acceptable dans une base hydroalcoolisée comprenant :

15 à 50% en poids de propylène glycol ;

20 à 40% en poids d'alcool isopropylique ;

20 à 60% en poids d'eau ;

0,1 à 0,5% en poids d'un agent épaississant et suffisamment de tampon pour maintenir le pH de la composition entre 3,0 et 8,0.

2. Lotion de la revendication 1, où le corticostéroïde comprend 0,02 à 0,2% en poids de la composition.

3. Lotion de la revendication 1, où le corticostéroïde est le bétaméthasone 17,21 dipropionate.

4. Lotion de la revendication 3, où le bétaméthasone 17,21-dipropionate est présent en une quantité de 0,064% en poids.

5. Lotion de la revendication 4 comprenant :

	Ingrédients	Concentration (mg/g)
40	Bétaméthasone 17,21-dipropionate USP	0,64*
45	Phosphate monobasique de sodium monohydraté R	2,00
	Acide phosphorique NF	**
	Soude R	**
	Propylène glycol USP	300,00
50	Alcool isopropylique USP	300,00
	Hydroxypropyl Cellulose NF	1,50
	Eau purifiée USP	s.q. jusqu'à 1,00 g

55 * Equivalent à 0,5 mg Bétaméthasone/g

** Utilisé pour ajuster le pH à $4,5 \pm 0,2$.

6. Lotion de la revendication 1, où le corticostéroïde est le dipropionate d'alclométasone.

7. Lotion de la revendication 6 comprenant :

5	<u>Ingrédients</u>	<u>Concentration</u>
		(mg/g)
	Dipropionate d'alclométasone	0,5
	Carbomer 940 [®]	2,60
10	Soude, R	0,04
	Propylène glycol, USP	200,0
	Alcool isopropylique, NF	300,0
15	Acide chlorhydrique	*
	Eau purifiée, USP s.q. jusqu'à	1,0 g
	* utilisé pour ajuster le pH à 4,5.	

20 8. Lotion de la revendication 1, où le corticostéroïde est le furoate de mométasone.

9. Lotion de la revendication 8 comprenant :

25	<u>Ingrédients</u>	<u>Concentration</u>
		(mg/g)
	Furoate de mométasone	1,0
	Alcool isopropylique USP	400,0
	Propylène Glycol USP	300,0
30	Hydroxypropyl Cellulose (Klucel HF [®])	1,5
	Phosphate monobasique de sodium monohydraté R	2,0
	Acide phosphorique NF	*
35	Eau purifiée USP s.q. jusqu'à	1 g
	* Utilisé pour ajuster le pH à 4,5 ± 0,1.	

40 10. Lotion de la revendication 1, où l'agent épaississant est un polymère d'acide acrylique.

11. Lotion de la revendication 1, où l'agent épaississant est l'hydroxypropyl cellulose.

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Applicant/Proprietor

SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth New Jersey
07033, United States of America [ADP No. 50348622002]

Inventors

A. JOEL SEQUEIRA, 18 Stuyvesant Oval, New York, NY 10009, United States of
America [ADP No. 57346272001]

J. FARAH MUNAYYER, 494 Passaic Avenue, West Caldwell, NJ 07006, United
States of America [ADP No. 57346280001]

REBECCA GALEOS, 18 Clinton Street, Bloomfield, NJ 07003, United States of
America [ADP No. 57346298001]

Classified to

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Address for Service

MATHYS & SQUIRE, 10 Fleet Street, London, EC4Y 1AY, United Kingdom
[ADP No. 00001081001]

EPO Representative

ALEK VON KREISLER, Patentanwälte von Kreisler Selting Werner Deichmannhaus
am Hauptbahnhof, D-5000 Köln 1, Federal Republic of Germany
[ADP No. 57147860001]

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Deichmannhaus am Hauptbahnhof, D-5000 Köln 1, Federal Republic of
Germany [ADP No. 57147860001]
to
ALEK VON KREISLER, Patentanwälte von Kreisler Selting Werner
Deichmannhaus am Hauptbahnhof, W-5000 Köln 1, Federal Republic of
Germany [ADP No. 57147860001]

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[ADP No. 00001081001]

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PROPRIETOR(S)

SCHERING CORPORATION, 2000 Galloping Hill Road, Kenilworth New
Jersey 07033, United States of America

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