1 563 757

PATENT SPECIFICATION

(11) 1 563 757

(21) Application No. 44073/77 (22) Filed 24 Oct. 1977
(31) Convention Application No. 735854
(32) Filed 26 Oct. 1976 in
(33) United States of America (US)
(44) Complete Specification published 2 April 1980
(51) INT CL³ A61K 9/10 31/57
(52) Index at acceptance
A5B 170 241 244 246 24Y 26Y 323 32Y 381 38Y 402 407 40Y J



(54) IMPROVED OINTMENT

(71) We, SHERICO LTD., of Topferstrassee 5, Lucerne, Switzerland, a Body Corporate constituted under the laws of Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a topical ointment for use in the application of 17-mono- and 17,21-diesters of betamethasone. More particularly, this invention relates to a new ointment vehicle for 17-mono- and 17,21-diesters of betamethasone.

The use of topical ointments as vehicles for steroid medicaments, particularly steroids having anti-inflammatory activity, is well-known in the art. The problem which must be dealt with in order to prepare a successful composition is to balance the completeness of incorporation of the steroidal medicament in the vehicle with the ease and completeness of its release from the ointment to and through the skin to which it is applied.

Topical steroids incorporated in oil-in-water or water-in-oil emulsion-based vehicles have been observed to remain unabsorbed by the skin because the steroid is insoluble in such systems. Alternatively, a water-soluble steroid may be used which does dissolve in the aqueous phase of either the oil-in-water or the water-in-oil emulsion base, but when the steroid is exposed to the dermal surface, it is too vehicle-soluble for optimal absorption.

Preferred bases for ointments are oleaginous bases which form an occlusive covering on the skin, thereby inducing skin hydration through sweat accumulation at the skin-ointment interface. Hydration is advantageous in that it restores suppleness to dry skin. However, the incorporation of topical steroids in such bases suffers from the same lack of absorption as with the emulsion type of ointment base. Ointment bases of this kind are also decreasing in favor because they are greasy and difficult to remove from the skin and clothing due to their lack of water-washability.

An optimum manner of effecting solubilization of topical steroids while obtaining good absorption is to completely dissolve the steroid in a pharmaceutical dosage form, but the steroid must have an optimal lipophilic/lipophobic ratio for optimal dermal absorption. at present, attempts to achieve this optimum lipophilic/lipophobic balance utilize the micronization of the water-insoluble steroid prior to or after incorporation into the oil-in-water or water-in-oil emulsified base or oleaginous base. However, the water content of such emulsion vehicles generally makes them less efficient in the release of the medicinal steroid to the patient's skin. Proper dispersion of the steroid in the oleaginous bases is also a problem that results in inefficient absorption.

In order to obviate the disadvantages of utilizing a water-containing composition, it has previously been found useful to formulate a steroid with a saturated fatty alcohol, a glycol solvent and a compatible plasticizer to give an anhydrous, water-deteriorable product (U.S. Patent 3,952,930). However, this type of composition lacks the good occlusive covering ability afforded by an oleaginous base since it is in the form of a fluid and is also subject to water-deterioration, *e.g.*, the sweat of the patient's skin.

The present invention, most surprisingly, provides an ointment having the occlusive properties of an oleaginous base with an improved washability while reducing the greasiness typical of standard oleaginous base ointments and the water-solubility of the saturated fatty alcohol based ointments. Surprisingly, this invention utilizes a water-miscible non-aqueous base which is a solvent-in-oil emulsion. This emulsion ointment functions as the prior art water-in-oil emulsions in that it provides the necessary lipophilic/lipophobic ratio needed for optimal dermal absorption of the steroid medicament, but lacks the detrimental

water content of such emulsions. Since the emulsion of this invention incorporates an oleaginous base it retains the desirable occlusivity and water-insolubility of such conventional ointments. However, it is rendered less greasy (hence, more cosmetically elegant) and more water-washable through the use of the non-aqueous, water-miscible solvent as the phase-in-oil and the emulsifiers added to form the emulsion. Additionally, and most surprisingly, the dermal absorption of the steroid medicament is increased by the improved lipophilic/lipophobic ratio which the composition of the present invention possesses.

This invention particularly relates to topical ointments for the treatment of dermatological disorders and which contain a steroid anti-inflammatory agent as the active ingredient. It also relates to methods of treating dermatological disorders in non-human animals in which such ointments are applied to the skin. The anti-inflammatory agents disclosed herein are of value in the topical treatment of inflammation or like conditions responsive to anti-inflammatory drugs. Included within this category are disorders such as psoriasis, contact dermatitis (dermatitis venenata), atopic dermatitis (infantile eczema, allergic dermatitis), neurodermatitis (lichen simplex chronicus), lichen planus, eczema (including nummular eczema, hand eczema, eczematons dermatitis), intertrigo, dyshidrosis (pompholyx), seborrheic dermatitis, exfoliative dermatitis, solar dermatitis, stasis dermatitis and anogenital and senile proritus.

Treatment with the ointments of this invention is usually accomplished by applying the ointment to completely cover the affected area. The usual frequency of application is twice daily, although adequate maintenance therapy for some patients may be achieved with less frequent application.

The ointment of the present invention comprises an amount effective to treat said dermatological disorders of a dermatologically acceptable 17-mono- or 17,21-diester of betamethasone in a water-miscible non-aqueous base which is a solvent-in-oil emulsion comprising by weight 5—15% of a non-aqueous, water-miscible solvent consisting essentially of a glycol solvent selected from 1,2-propylene glycol (1,2-propanediol), butylene glycol (1,3-butanediol and 2,3-butanediol), hexylene glycol (2-methyl-2,4-pentanediol) and mixtures thereof, 1—3% of propylene glycol monostearate, 0—7% of white or yellow wax and 70—90% of petrolatum. Preferably the base of this ointment consists essentially of a glycol solvent selected from 1,2-propylene glycol, butylene glycol, hexylene glycol and mixtures thereof, and propylene glycol monostearate, white or yellow max and petrolatum. Therein the propylene glycol monostearate serves as the principal emulsifying agent, the white or yellow wax as the secondary emulsifying agent.

The ointments of the present invention contain the steroid medicament in a therapeutically effective amount, *e.g.*, an amount by weight of from 0.0005 to 5% of the total composition. Ranges of 0.005 to 0.5% are particularly suitable with a range of 0.01—0.2% by weight being most preferable, especially with a range of 0.06—0.13% by weight.

The preferred steroid ingredients for use in the composition of the present invention are the dermatologically acceptable 17-mono and 17,21-diesters of betamethasone disclosed in U.S. Patents 3,312,590 and 3,529,060. Particularly preferred steroids are betamethasone 17,21-dipropionate and betamethasone 17-valerate. Another preferred steroid is betamethasone 17-benzoate.

The glycol or mixture of glycols functions as the sole solvent of the betamethasone esters. The glycol solvent and steroid and the proportions thereof are preferably selected so that the concentration of steroid in the glycol solvent is at or substantially at the saturation point of the steroid in the chosen glycol solvent. Propylene glycol is the most preferred solvent.

The primary emulsifying agent is propylene glycol monostearate, a compatible, pharmaceutically acceptable emulsifying agent. It is preferably present in an amount of 1—2% by weight of the formulation. The secondary emulsifying agent, white or yellow wax, is present in an amount of 0—7% by weight. The secondary emulsifying agent may be omitted, but its use is desirable to obtain a formulation with a suitable melting point. A formulation containing about 6% by weight white wax is particularly suitable since this affords an ointment usable in the warmer climates. White wax (USP) is preferred over yellow wax (NF) since it affords a more appealing product. However, the white and yellow waxes are equivalent for the purposes of the invention.

The composition of the present invention may also contain incidental pharmaceutical adjuvants, preferably not more than 10% by weight. These adjuvants may be added to improve consistency, homogeneity, spreadability, texture and appearance of the ointment.

Usually in the ointment the petrolatum is present in an amount of 80—90% by weight.

The ointment of the present invention is

manufactured in a conventional manner by thoroughly mixing the ingredients, suitably at an ambient or elevated temperature. Preferably, the steroid is first dissolved in the glycol solvent which is then mixed with the remaining ingredients.

If desired, additional mechanical agitation can be used as an intermediate or final step in the manufacturing process to impart more homogeneity or improve texture. Processing equipment suitable for these steps is known and includes heat exchangers, propeller mixers, colloid mills, homogenizers, roller mills and the like.

The following examples describe in detail compositions and methods illustrative of the present invention. It will be apparent to those skilled in the art that many modifications, both of materials and methods, may be practiced without departing from the scope of the claims.

EXAMPLE 1
Betamethasone Dipropionate Ointment

Ingredients	mg/g
Betamethasone 17,21-dipropionate	0.64*
Propylene Glycol Monostearate	20.00
Propylene Glycol USP (1,2-propylane diol)	100.00
White Wax USP	60.00
White Petrolatum USP	819.36

* equivalent to 0.5 mg betamethasone

Procedure

Heat the propylene glycol to about 50°C. Dissolve the betamethasone dipropionate in the propylene glycol using a moderate-speed agitator. Heat and melt the white petrolatum, white wax and propylene glycol monostearate together in a stainless steel bowl equipped with a moderate-speed mixer. Stir until the mixture is uniform and continue heating to 65—70°C. Strain through 80-mesh screen into stainless steel bowl equipped with moderate-speed agitator and keep the temperature at about 60°C. Charge the propylene glycol solution into the oily mixture using moderate-speed agitation during the addition. Continue mixing for about 15 minutes while maintaining the temperature of about 55—60°C. Mix while cooling to 30°C or until the ointment solidifies completely. Package in suitable tubes for dispensing.

EXAMPLE 2
Betamethasone Valerate Ointment

Ingredients	
Betamethasone 17-valerate	1.275 mg/g*
Propylene Glycol USP (1,2-propanediol)	60.00 mg/g
Propylene Glycol Monostearate	10.00 mg/g
White Wax USP or Yellow Wax NF	60.00 mg/g
White Petrolatum USP	q.s. 1.00 g

*equivalent to 1.05 mg betamethasone

Procedure

The procedure detailed in Example 1 is followed using the betamethasone 17-valerate in place of the betamethasone 17,21-dipropionate.

The ointments of the present invention have been found to be self-preserving when tested in standardized assays for the determination of growth of *Escherichia coli, Candida albicans, Staphylococcus aureus, Aspergillis niger,* and *Pseudomonas aeruginosa.* Thus, in most cases, no additional preservatives are necessary to the formulation.

In view of test results it can be concluded that the ointments of the present invention are unexpectedly superior to previously known vehicles for use with topical steroids. For example, in preliminary tests, betamethasone dipropionate in the vehicle of this invention has been observed to have greater activity in comparison to its activity in the standard vehicle at the same concentration. This fact is further supported by the following experiment:

An ointment of the present invention as prepared in Example 1 was tested in a bilateral paired psoriasis study using a conventional betamethasone 17,21-dipropionate ointment consisting of 0.64 mg/g betamethasone 17,21-dipropionate, 50.0 mg/g mineral oil and 949.36 mg/g white petrolatum. In this test 41 patients suffering from chronic, stubborn psoriasis were tested. Half of the patients received the ointment of Example 1 on the right lesions and the other half on the left. A thin layer of the ointments was applied twice daily without occlusion to areas selected by the investigator. This treatment was carried out during 2 weeks. At two visits after the initial treatment the treated areas were checked by the investigator and his and the patient's opinion were recorded. Results of the bilateral paired comparison study [P values based on two-tailed sign test] indicate the ointment of Example 1 to be significantly ($p \leq 0.05$) more effective than the conventional ointment in the treatment of patients with chronic, stubborn psoriasis, based on the following results:

1. The proportion of results favoring the ointment as prepared in Example 1, based on comparison of severity of treated sides, was significantly ($p \leq 0.01$, two-tailed) greater than the proportion favoring the conventional ointment for: erythema, induration, scaling, total symptom score,

patient's global opinion ($p \leq 0.02$), and physician's global opinion.

2. Mean severity of erythema, induration, scaling and total symptom score was significantly less ($p \leq 0.05$) for the ointment prepared as in Example 1.

3. Mean percent reduction in severity of erythema, induration, scaling and total symptom score was significantly less for the ointment prepared as in Example 1.

WHAT WE CLAIM IS:—

1. A topical ointment for the treatment of dermatological disorders which comprises an amount effective to treat said dermatological disorders of a dermatologically acceptable 17-mono- or 17,21-diester of betamethasone in a watermiscible non-aqueous base which is a solvent-in-oil emulsion comprising by weight

5—15% of a non-aqueous, water-miscible solvent consisting essentially of a glycol solvent selected from 1,2-propylene glycol, butylene glycol, hexylene glycol and mixtures thereof,

1—3% of propylene glycol monostearate,

0—7% of white or yellow wax and,

70—90% of petrolatum.

2. The ointment according to Claim 1, the base of which consists essentially of a glycol solvent selected from 1,2-propylene glycol, butylene glycol, hexylene glycol and mixtures thereof, and propylene glycol monostearate, white or yellow wax and petrolatum.

3. The ointment according to Claim 1 or 2 containing incidental pharmaceutical adjuvants.

4. The ointment of any one of Claims 1 to 3, wherein the betamethasone ester is betamethasone 17-valerate.

5. The ointment of any one of Claims 1 to 3, wherein the betamethasone ester is betamethasone 17,21-dipropionate.

6. The ointment of any one of Claims 1 to 5, wherein the betamethasone ester is present in an amount of from 0.005 to 5% by weight.

7. The ointment of Claim 6, wherein the betamethasone ester is present in an amount of 0.01 to 0.2% by weight.

8. The ointment of Claim 6, wherein the betamethasone ester is present in an amount of 0.06 to 0.13% by weight.

9. The ointment of any one of Claims 1 to 8, wherein the solvent is 1,2-propylene glycol.

10. The ointment of any one of Claims 1 to 9, wherein the glycol solvent is present in an amount such that the concentration of the betamethasone ester in the glycol is at or is substantially at the saturation point of the betamethasone ester in the glycol.

11. The ointment of any one of Claims 1 to 10, wherein the wax is white wax.

12. The ointment of any one of Claims 1 to 11, wherein the wax is present in an amount of about 6% by weight.

13. The ointment of any one of Claims 1 to 12, wherein the propylene glycol monostearate is present in an amount of 1—2% by weight.

14. The ointment of any one of Claims 1 to 13, wherein the petrolatum is present in an amount of 80—90% by weight.

15. The ointment according to Claim 1 consisting by weight of 0.0064% betamethasone, 17,21-dipropionate, 2.000% propylene glycol monostearate, 10.000% propylene glycol (USP), 6.000% white wax (USP) and 81.936% white petrolatum (USP).

16. An ointment as claimed in claim 1 and substantially as herein before described.

17. A method of treating dermatological disorders which comprises applying to the skin of a nonhuman animal an ointment according to any one of Claims 1 to 16.

18. The method of Claim 17, wherein the dermatological disorder is an inflammation.

19. The method of Claim 17, wherein the dermatological disorder is psoriasis.

20. A process for preparing an ointment as claimed in any one of Claims 1 to 16, useful in the treatment of dermatological disorders which comprises mixing the ingredients specified in any one of Claims 1 to 16.

21. An ointment, when prepared by the process of Claim 20.

MATHYS & SQUIRE,
Chartered Patent Agents,
10 Fleet Street,
London, E.C.4.,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

patient's global opinion ($p \leq 0.02$), and physician's global opinion.

2. Mean severity of erythema, induration, scaling and total symptom score was significantly less ($p \leq 0.05$) for the ointment prepared as in Example 1.

3. Mean percent reduction in severity of erythema, induration, scaling and total symptom score was significantly less for the ointment prepared as in Example 1.

WHAT WE CLAIM IS:—

1. A topical ointment for the treatment of dermatological disorders which comprises an amount effective to treat said dermatological disorders of a dermatologically acceptable 17-mono- or 17,21-diester of betamethasone in a watermiscible non-aqueous base which is a solvent-in-oil emulsion comprising by weight

5—15% of a non-aqueous, water-miscible solvent consisting essentially of a glycol solvent selected from 1,2-propylene glycol, butylene glycol, hexylene glycol and mixtures thereof,

1—3% of propylene glycol monostearate,

0—7% of white or yellow wax and,

70—90% of petrolatum.

2. The ointment according to Claim 1, the base of which consists essentially of a glycol solvent selected from 1,2-propylene glycol, butylene glycol, hexylene glycol and mixtures thereof, and propylene glycol monostearate, white or yellow wax and petrolatum.

3. The ointment according to Claim 1 or 2 containing incidental pharmaceutical adjuvants.

4. The ointment of any one of Claims 1 to 3, wherein the betamethasone ester is betamethasone 17-valerate.

5. The ointment of any one of Claims 1 to 3, wherein the betamethasone ester is betamethasone 17,21-dipropionate.

6. The ointment of any one of Claims 1 to 5, wherein the betamethasone ester is present in an amount of from 0.005 to 5% by weight.

7. The ointment of Claim 6, wherein the betamethasone ester is present in an amount of 0.01 to 0.2% by weight.

8. The ointment of Claim 6, wherein the betamethasone ester is present in an amount of 0.06 to 0.13% by weight.

9. The ointment of any one of Claims 1 to 8, wherein the solvent is 1,2-propylene glycol.

10. The ointment of any one of Claims 1 to 9, wherein the glycol solvent is present in an amount such that the concentration of the betamethasone ester in the glycol is at or is substantially at the saturation point of the betamethasone ester in the glycol.

11. The ointment of any one of Claims 1 to 10, wherein the wax is white wax.

12. The ointment of any one of Claims 1 to 11, wherein the wax is present in an amount of about 6% by weight.

13. The ointment of any one of Claims 1 to 12, wherein the propylene glycol monostearate is present in an amount of 1—2% by weight.

14. The ointment of any one of Claims 1 to 13, wherein the petrolatum is present in an amount of 80—90% by weight.

15. The ointment according to Claim 1 consisting by weight of 0.0064% betamethasone, 17,21-dipropionate, 2.000% propylene glycol monostearate, 10.000% propylene glycol (USP), 6.000% white wax (USP) and 81.936% white petrolatum (USP).

16. An ointment as claimed in claim 1 and substantially as herein before described.

17. A method of treating dermatological disorders which comprises applying to the skin of a nonhuman animal an ointment according to any one of Claims 1 to 16.

18. The method of Claim 17, wherein the dermatological disorder is an inflammation.

19. The method of Claim 17, wherein the dermatological disorder is psoriasis.

20. A process for preparing an ointment as claimed in any one of Claims 1 to 16, useful in the treatment of dermatological disorders which comprises mixing the ingredients specified in any one of Claims 1 to 16.

21. An ointment, when prepared by the process of Claim 20.

MATHYS & SQUIRE,
Chartered Patent Agents,
10 Fleet Street,
London, E.C.4.,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.