PATENT SPECIFICATION (11) 1 589 224

1 589 224

(21) Application No. 37156/77 (22) Filed 6 Sep. 1977 (19)

(31) Convention Application No. 720835 (32) Filed 7 Sep. 1976 in

(33) United States of America (US)

(44) Complete Specification Published 7 May 1981

(51) INT. CL.[3] A61K 7/48

(52) Index at Acceptance

A5B 170 26Y 285 28Y 38Y 39X 401 402
403 40Y 411 41Y 421 422 423 42Y
FH H

(54) COSMETIC COMPOSITIONS FOR THE TREATMENT OF DRY SKIN

(71) We, EUGENE JOSEPH VAN SCOTT, of 1138 Sewell Lane, Rydal, Pennsylvania 19046, United States of America, and RUEY & JIIN YU, of 4400 Dexter Street, Philadelphia, Pennsylvania 19128, United States of America, both citizens of the United States of America, 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 cosmetic treatment for skin disorders characterized by cracking, flaking or scaling of hands, feet or the body commonly known as "dry skin", and specifically to compositions containing compounds which have been found to be effective when topically applied to prevent as well as heal the skin lesions associated with these conditions in humans.

Severe "dry skin" conditions known as ichthyosis are hereditary disorders. The term ichthyosis alludes to a fish scale-like appearance of the human skin. Ichthyosis, characterized by a "dry skin" appearance, is usually detected during the early years of childhood. Small, fine scales with a "pasted-on" appearance are found most prominently on the trunk and upper extremities. Larger, more adherent scales are present on the legs. Only a small number of the population are affected by this hereditary disorder.

In contrast to ichthyosis, mild to moderate "dry skin" conditions are quite common among the population. These common "dry skin" conditions are specially pronounced during the fall and winter seasons, when environmental humidity is comparatively low. They are characterized by fissures, chaps, cracks or flakes of the skin on hands, face, neck and legs.

Conventional treatments for all kinds of dry skin conditions primarily involve the topical application of oils or oil preparations, and hydrating emollients. In addition, ointments containing salicyclic acid, urea, glycerol, propylene glycol, sorbitol or vitamin A have been used. Prior treatments, however, have not been universally successful, and have, in many cases, been unable to promote healing to cause a complete remission of the symptoms. Because the mechanisms involved in causing dry skin are not known, treatment has usually resulted in only a temporary remission or healing of the flaky or scaly lesions.

We have now discovered that "dry skin" conditions may be successfully prevented or treated by application of compositions comprising the reaction products of certain acids and their derivatives and certain bases.

Specifically, we have discovered that the symptoms of dry skin in humans may be alleviated by the topical administration of a therapeutically effective amount of a composition comprising the reaction product of A) at least one reactant selected from citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone, α-hydroxy-buryric acid, α-hydroxyisobutyric acid, lactic acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, β-phenyllactic acid, β-phenylpyruvic acid, saccharic acid, tartaric acid, tartronic acid, and -hydroxybutyric acid, and B) a base selected from ammonium hydroxide, organic primary, secondary, or tertiary alkylamides, alkanol amines, diamines, dialkylamines, dialkanolamines, alkylalkanol amines, trialkylamines, trialkanol amines, dialkyl alkanol amines, or alkyl dialkanolamines wherein the alkyl or alkanol substituent has from 1 to 8 carbon atoms and the or each alkanol substituent has one -OH group; in a pharmaceutically acceptable vehicle.

According to the present invention we provide a cosmetic composition comprising as

SPECIFICATION AMENDED - SEE ATTACHED SLIP

active ingredient the reaction product as defined above together with a pharmacentically acceptable vehicle but excluding simple solutions of said reaction product in water or common solvents.

In a preferred embodiment of this invention, we provide a composition comprising the reaction product of A) as defined above and B) a base selected from ammonium hydroxide, methylamine, ethylamine, monoethanolamine, monoisopropanolamine, ethylenediamine, 1,2-diamino-propane, dimethylamine, diethylamine, diethanolamine, diisopropanolamine, N-methylethanolmine, N-ethylethanolamine, triethylamine, triethanolamine, N-methyldiethanolamine, and triisopropylamine, in a pharmaceutically acceptable vehicle.

It has been established through tests on humans having "dry skin" conditions that topical application of a lotion, cream or ointment containing from 1 to 20 percent by volume of the reaction product described above and preferably from 2 to 10 percent thereof, is therapeutically effective, when applied on a regular basis, to cause, within about one to two weeks, a return of the affected areas to a normal skin conditions. If two or more reaction products are used in a composition of the invention, the total concentration of the products is preferred not to exceed 10 precent by weight of the composition. It has also been found in humans having frequent occurrence of cracking or flaking skin that topical application of the aforementioned composition of the present invention is effective, when applied on a regular basis, in preventing development of dry skin lesions.

Generally, the compositions used in this invention should have a pH of between 3.5 and 7.5.

We have found that the invention provides a composition suitable for safe and efficient treatment the symptoms of dry skin through regular topical application of a composition as defined above which will promote healing within about one to two weeks.

The composition may be formulated as a lotion, cream or ointment which when topically applied at least daily to skin areas prone to lesions of cracking, flaking or scaling will prevent the development of dry skin or result in a restoration of normal healthy skin condition.

Preparation of the therapeutic compositions

Previously, the treatment of extremely dry skin conditions such as ichthyosis, α- or β-hydroxyacids or α-keto-acids were prepared in a composition containing 5 to 10 percent by weight of the compounds in a cream or ointment. The pH of the composition was 2 or less. In treatment of common dry skin conditions using compositions according to this invention, we found that the above composition with low pH could cause some skin irritation (redness and sensation of burning) on some of the sensitive subjects. It was therefore desirable to develop compositions in accordance with the present invention which were therapeutically effective but not irritative.

The reaction product of the compositions of the present invention is prepared by reacting the appropriate reactant A) as defined above in a solvent with a base B) as defined above.

The solvent used in the reaction is one or more selected from water, alcohol, ether and acetone. The preferred solvent is water. The concencentration of solvent used in the reaction is usually from 5 to 30 percent by volume.

The reaction may conveniently be carried out at temperatures of from 0°C to 75°C. It is preferred to carry out the reaction at room temperature.

In a preferred embodiment the reaction product comprises from 1 to 20 percent by volume of the total composition.

In a further preferred embodiment the reaction product comprises from 2 to 10 percent by volume of the total composition.

The compositions of the present invention include those comprising two or more than two different reaction products.

The prophylactic and therapeutic composition may be prepared in a form of lotion, cream or ointment and in these instances, cosmetically acceptable ingredients are incorporated into the formulation.

Example 1

Glycolic acid, 5 grams was dissolved in 10 ml water and ethanolamine, 3 ml was added to partially neutralize the acidity of the solution. This solution was admixed with 82 grams of water-insoluble lotion prepared from mineral oil, cottonseed oil, isopropyl palmitate and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 15:15:5:60:5 parts by weight, respectively. The lotion thus prepared is stored in a plastic squeeze bottle having a nozzle attached thereto.

Example 2

Lactic acid, USP grade 5 ml, was dissolved in 10 ml of water and triethanolamine, 5 ml. was added to neutralize partially the acidity of the solution. This solution was admixed with 80 grams of water-insoluble lotion prepared from mineral oil, cottonseed oil and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 30:15:50:5 parts by weight, respectively.

Example 3

Part A:	Polyoxyethylene (20) sorbitan mono-oleate (hereinafter Tween 80 - "Tween" is a registered trade mark)	5 gm
	Cetyl alcohol	20 gm
Part B:	Water	45 ml
	Propylene glycol	10 ml
	Glycolic acid	10 gm
	Ethanolamine	7 ml

Heat Part A to 75°C and heat Part B to 75°C. Add Part B slowly to Part A with agitation. Continue agitation until the mixture is congealed. The water-washable cream thus prepared has a pH of 4.7.

Example 4

Part A:	Tween 80	5 gm
	Cetyl alcohol	22 gm
Part B:	Water	55 ml
	Propylene glycol	10 ml
	Lactic acid	5 ml
	Ethanolamine	2 ml

Heat Part A to 75°C and heat Part B to 75°C. Add Part B slowly to Part A with agitation. Continue agitation until the mixture is congealed. The water-washable cream thus prepared has a pH of 4.5.

Example 5

Part A:	Tween 80	5 gm
	Cetyl alcohol	15 gm
	Stearyl alcohol	5 gm
Part B:	Water	60 ml
	Propylene glycol	5 ml
	Citric acid	2 gm
	Lactic acid	2 ml
	Glycolic acid	2 gm
	Ethanolamine	3 ml

Heat both Part A and Part B to 75°C. Add Part B slowly to Part A with agitation. Continue agitation until the mixture is congealed. The water-washable cream containing three active ingredients as ethanolamine salts has a pH of 4.4.

Example 6

Glycolic acid, 7 grams was dissolved in 10 ml of ice water and ethanolamine, 5 ml was added to neutralize partially the acidity of the solution. This solution was admixed with 78 grams of water-insoluble ointment prepared from petrolatum, mineral oil, spermaceti and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 10:10:6:68:6 parts by weight, respectively.

Example 7

Lactic acid, USP grade 5 ml was dissolved in 10 ml of ice water and triethanolamine, 4 ml was added to neutralize partially the acidity of the solution. This solution was admixed with 81 grams of water-insoluble ointment prepared from petrolatum, mineral oil, isopropyl myristate, spermaceti and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 10:10:10:6:58:6 parts by weight, respectively.

TEST RESULTS

(A) *Severe Dry Skin*

Ten patients with severe dry skin conditions such as ichthyosis were instructed first to wet the body by taking a shower and then apply a thin film of the compositions formulated according to Examples 4 or 7 on left side of the body. Other commercially available preparations such as vegetable oil or petrolatum were applied on right side of the body. Twice daily topical application was continued for several weeks. In all the patients tested the left side of the body became less flaky and felt smoother than the right side after about a week of topical treatment. The rough and flaky lesions on the left side of the body were substantially clear after ten days of treatment. The left side of the body devoid of any cracking, flaking or scaling usually reached an improved state comparable to normal appearing skin within two to three weeks after initial treatment. Very little or no substantial improvement was seen of the right side of the body, which had been treated with vegetable oil or petrolatum alone. Therefore after three weeks the patients were instructed to apply the composition of the present invention on the right side of the body. Again, the skin on the right side of the body became normal appearing within two to three weeks.

Once a normal appearing skin was restored, it remained improved for from several weeks to several months, varying from patient to patient, without further application of the ointment. It was, however, necessary to continue the application of the ointment in order to maintain the skin free from recurrence of the overt disease.

(B) *Common Dry Skin*

Human subjects with mild to moderate degrees of dry skin conditions, as evidenced by dry, cracking or flaking of the skin, were instructed to apply topically the lotion, cream or ointment of the present invention formulated according to Examples 1 to 7 on the affected skin areas. Twice daily topical application was continued for a few weeks. In all the twenty-three human subjects tested the feeling of the skin dryness disappeared after three to four days of topical treatment. In twenty-one human subjects tested the rough and cracked skin usually became less pronounced within a weeks time. Generally the skin appeared normal and felt smooth after about two weeks of topical treatment.

In contrast to the severe dry skin disease the common dry skin conditions once restored to normal appearing skin remained improved for some time until causes of dry skin, such as low humidity, cold weather, detergents, soaps, chemicals, etc., recurred. On continued use it was also found that twice daily topical application of a composition of the present invention prevented the development of new dry skin lesions.

WHAT WE CLAIM IS:

1. A cosmetic composition for alleviating the symptoms of dry skin in humans comprising as active ingredient the reaction product of

A) at least one reactant selected from citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone, α-hydroxybutyric acid, α-hydroxyisobutyric acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, β-phenyllactic acid, β-phenylpyruvic acid, saccharic acid, tartaric acid, tartronic acid, and β-hydroxybutyric acid, and

B) a base selected from ammonium hydroxide, and organic primary, secondary, or tertiary alkylamines, alkanol amines, diamines, dialkylamines, dialkanolamines, alkylalkanol amines, trialkylamines, trialkanol amines, dialkyl alkanol amines, and alkyl dialkanolamines wherein the alkyl or alkanol substituent has from 1 to 8 carbon atoms and the or each

Heat both Part A and Part B to 75°C. Add Part B slowly to Part A with agitation. Continue agitation until the mixture is congealed. The water-washable cream containing three active ingredients as ethanolamine salts has a pH of 4.4.

Example 6

Glycolic acid, 7 grams was dissolved in 10 ml of ice water and ethanolamine, 5 ml was added to neutralize partially the acidity of the solution. This solution was admixed with 78 grams of water-insoluble ointment prepared from petrolatum, mineral oil, spermaceti and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 10:10:6:68:6 parts by weight, respectively.

Example 7

Lactic acid, USP grade 5 ml was dissolved in 10 ml of ice water and triethanolamine, 4 ml was added to neutralize partially the acidity of the solution. This solution was admixed with 81 grams of water-insoluble ointment prepared from petrolatum, mineral oil, isopropyl myristate, spermaceti and water with a surfactant such as sorbitan sesquioleate, present in a ratio of 10:10:10:6:58:6 parts by weight, respectively.

TEST RESULTS

(A) *Severe Dry Skin*

Ten patients with severe dry skin conditions such as ichthyosis were instructed first to wet the body by taking a shower and then apply a thin film of the compositions formulated according to Examples 4 or 7 on left side of the body. Other commercially available preparations such as vegetable oil or petrolatum were applied on right side of the body. Twice daily topical application was continued for several weeks. In all the patients tested the left side of the body became less flaky and felt smoother than the right side after about a week of topical treatment. The rough and flaky lesions on the left side of the body were substantially clear after ten days of treatment. The left side of the body devoid of any cracking, flaking or scaling usually reached an improved state comparable to normal appearing skin within two to three weeks after initial treatment. Very little or no substantial improvement was seen of the right side of the body, which had been treated with vegetable oil or petrolatum alone. Therefore after three weeks the patients were instructed to apply the composition of the present invention on the right side of the body. Again, the skin on the right side of the body became normal appearing within two to three weeks.

Once a normal appearing skin was restored, it remained improved for from several weeks to several months, varying from patient to patient, without further application of the ointment. It was, however, necessary to continue the application of the ointment in order to maintain the skin free from recurrence of the overt disease.

(B) *Common Dry Skin*

Human subjects with mild to moderate degrees of dry skin conditions, as evidenced by dry, cracking or flaking of the skin, were instructed to apply topically the lotion, cream or ointment of the present invention formulated according to Examples 1 to 7 on the affected skin areas. Twice daily topical application was continued for a few weeks. In all the twenty-three human subjects tested the feeling of the skin dryness disappeared after three to four days of topical treatment. In twenty-one human subjects tested the rough and cracked skin usually became less pronounced within a weeks time. Generally the skin appeared normal and felt smooth after about two weeks of topical treatment.

In contrast to the severe dry skin disease the common dry skin conditions once restored to normal appearing skin remained improved for some time until causes of dry skin, such as low humidity, cold weather, detergents, soaps, chemicals, etc., recurred. On continued use it was also found that twice daily topical application of a composition of the present invention prevented the development of new dry skin lesions.

WHAT WE CLAIM IS:

1. A cosmetic composition for alleviating the symptoms of dry skin in humans comprising as active ingredient the reaction product of

A) at least one reactant selected from citric acid, glycolic acid, glucuronic acid, galacturonic acid, glucuronolactone, gluconolactone, α-hydroxybutyric acid, α-hydroxyisobutyric acid, malic acid, mandelic acid, mucic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, β-phenyllactic acid, β-phenylpyruvic acid, saccharic acid, tartaric acid, tartronic acid, and β-hydroxybutyric acid, and

B) a base selected from ammonium hydroxide, and organic primary, secondary, or tertiary alkylamines, alkanol amines, diamines, dialkylamines, dialkanolamines, alkylalkanol amines, trialkylamines, trialkanol amines, dialkyl alkanol amines, and alkyl dialkanolamines wherein the alkyl or alkanol substituent has from 1 to 8 carbon atoms and the or each

* C L M S *

alkanol substituent has one -OH group, together with a pharmaceutically acceptable vehicle but excluding simple solutions of said reaction product in water or common solvents.

2. A cosmetic composition according to Claim 1 comprising the reaction product of A) as defined in Claim 1 with B) a base selected from ammonium hydroxide, methylamine, ethylamine, monoethanolamine, monoisopropanolamine, ethylenediamine, 1,2-diaminopropane, dimethylamine, diethylamine, diethanolamine, diisopropanolamine, N-methylethanolamine, N-ethylethanolamine, triethylamine, triethanolamine, N-methyldiethanolamine, and triisopropylamine.

3. A cosmetic composition according to Claim 1 or 2 having a pH of from 3.5 to 7.5.

4. A cosmetic composition according to Claim 1, 2 or 3 wherein the reaction product is present in a concentration of from 1 up to 20 percent by volume of the total composition.

5. A cosmetic composition according to Claim 4 wherein the reaction product is present in a concentration of from 2 up to 10 percent by volume of the total composition.

6. A cosmetic composition according to any one of Claims 1 to 5 comprising per 100 parts by volume: a reaction product of 5 parts by weight glycolic acid and 3 parts by volume ethanolamine in a vehicle of mineral oil, cottonseed oil, isopropyl palmitate, water and a surfactant, present in a ratio of 15:15:5:60:5 parts by weight, wherein parts by weight and parts by volume are in the ratio of grams to milliliters.

7. A cosmetic composition according to any one of Claims 1 to 5 comprising per 100 parts by volume: a reaction product of 10 parts by weight glycolic acid and 7 parts by volume ethanolamine in 20 parts by weight cetyl alcohol, 5 parts by weight polyoxyethylene (2) sorbitan monooleate, 45 parts by volume water, and 10 parts by volume propylene glycol, wherein parts by weight and parts by volume are in the ratio of grams to milliliters.

8. A cosmetic composition according to any one of Claims 1 to 5 comprising per 100 parts by volume: a reaction product of 7 parts by weight glycolic acid and 5 parts by volume ethanolamine in 10 parts by volume water in a vehicle of petrolatum, mineral oil, spermaceti, water, and a surfactant, present in a ratio of 10:10:6:68:6 parts by weight wherein parts by weight and parts by volume are in the ratio of grams to milliliters.

9. A cosmetic composition according to Claim 1, substantially as described herein with reference to any one of Examples 1 to 7.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1981.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained

he affected
In all the
after three
rough and
ly the skin
:nt.
ce restored
kin, such as
ntinued use
he present

in humans

ronic acid,
: acid, α-
id, methyl
:id, tartaric

:ondary, or
, alkylalka-
dialkanola-
the or each

PATENTS ACT 1949

SPECIFICATION NO. 1589224

The following amendments were allowed under Section 29 on 1 February 1984.

Page 1, line 37, *for* buryric *read* butyric

Page 1, line 39, *for* –hydroxybutyric *read* β – hydroxybutyric

Page 1, line 41, *for* alkylamides *read* alkylamines

Page 2, line 24, *after* treatment *insert* of

Page 4, line 59, *after* acid, first occurrence *insert* lactic acid,

THE PATENT OFFICE
1 March 1984

Bas 255846/9