FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

620870

APPLICATION FOR A STANDARD PATENT

I\We,

UNILEVER PLC

of UNILEVER HOUSE
BLACKFRIARS
LONDON EC4
ENGLAND

hereby apply for the grant of a standard patent for an invention entitled AQUEOUS COMPOSITIONS OF PYROGLUTAMIC ACID ESTERS FOR TOPICAL APPLICATION TO HUMAN SKIN AND HAIR --

which is described in the accompanying complete specification

Details of basic application(s):

Number of basic application	Name of Convention country in which basic application was filed	Date of basic application
8811408.7	GB	13 MAY 88

My/our address for service is care of GRIFFITH HACK & CO., Patent Attorneys, 601 St. Kilda Road, Melbourne 3004, Victoria, Australia.

DATED this 10th day of May 1989

UNILEVER PLC

GRIFFITH HACK & CO.

TO: The Commissioner of Patents.

M 008896 100589

AUSTRALIAN PATENT OFFICE LS

Australia Patent Declaration Form

Forms 7 and 8 J307S(L)

AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

Name(s) of Applicant(s)

In support of the application made by UNILEVER PLC

Title

for a patent for an invention entitled COSMETIC COMPOSITION

Name(s) and address(es) of person(s) making declaration

I/~~We~~, Dilshad Rajan,
of Unilever House, Blackfriars, London EC4, England,

do solemnly and sincerely declare as follows:-

1. I am/~~we are the applicant(s) for the patent, or~~ authorised by the abovementioned applicant to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) by the following applicant(s) namely:-

Country, filing date and name of Applicant(s) for the or each basic application

in Great Britain on 13 May 19 88
by UNILEVER PLC
in _____ on _____ 19 ____
by _____

3. The said basic application(s) was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Name(s) and address(es) of the or each actual inventor

4. The actual inventor(s) of the said invention is/are Ian Richard SCOTT a British subject of 6 Hoylake, Wellingborough, Northants NN8 3NZ, England

See reverse side of this form for guidance in completing this part

5. The facts upon which the applicant(s) is/~~are~~ entitled to make this application are as follows:-

The applicant would be entitled to have assigned to it a patent granted to the actual inventor in respect of the said invention.

DECLARED at London, England, this 5th day of May 19 89

E O'Regan

(12) PATENT ABRIDGMENT (11) Document No. AU-B-34597/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 620870

(54) Title
AQUEOUS COMPOSITIONS OF PYROGLUTAMIC ACID ESTERS FOR TOPICAL APPLICATION TO HUMAN SKIN

International Patent Classification(s)
(51)* **A61K 031/40** **A61K 007/48**

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(71) Applicant(s)
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(72) Inventor(s)
IAN RICHARD SCOTT

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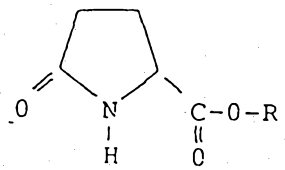
GRIFFITH HACK & CO , GPO Box 1285K, MELBOURNE VIC 3001

(56) Prior Art Documents
EP 176217

(57) Claim

1. An aqueous composition for topical application to human skin which comprises:

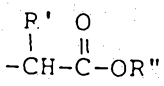
(i) from 0.01 to 99% by weight of an ester of pyroglutamic acid having the structure:



(1)

where R is a linear or branched chain saturated or unsaturated alkyl group having from 1 to 12 atoms,

or the group:



where R' and R" are the same or different and are each represented by H or the group:

$$[(CH_3)_u,(CH_2OH)_v,(CH_2)_w,(CHCH_3)_x,(CHOH)_y,(CH{=}CH)_z] \quad (2)$$

.../2

where either u or v is 1 and the other of t , is zero
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4
y is zero, or an integer of from 1 to 2
z is zero, or an integer of from 1 to 4; and
u + v + w + x + y + z is an integer of from 1 to 22;

the subgroups within the group (2) being in any sequence; provided that when the subgroup (CH=CH) is present, then the total number of carbon atoms in said group (2) will be from 10 to 20; and

(ii) from 1 to 99.99% by weight of a cosmetically acceptable aqueous buffer having an effective pH of from 2 to <7; and

(iii) from 0 to 98.99% by weight of cosmetic adjuncts.

AUSTRALIA

PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

620870

Short Title:

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Application Number:
Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:
UNILEVER PLC

Address of Applicant: UNILEVER HOUSE
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Actual Inventor:

Address for Service: GRIFFITH HACK & CO.,
601 St. Kilda Road,
Melbourne, Victoria 3004,
Australia.

Complete Specification for the invention entitled:
~~COSMETIC COMPOSITION~~

The following statement is a full description of this invention including the best method of performing it known to me:-

AQUEOUS COMPOSITIONS OF PYROGLUTAMIC ACID ESTERS FOR TOPICAL APPLICATION TO HUMAN SKIN AND HAIR --

COSMETIC COMPOSITION

FIELD OF INVENTION

The invention relates to aqueous compositions containing an ester of pyroglutamic acid for topical application to human skin or hair.

BACKGROUND AND PRIOR ART

Pyroglutamic acid (also known as 2-pyrrolidone-5-carboxylic acid) is the principle ingredient of the "natural moisturising factor" that enables the stratum corneum of the skin to maintain a high water content despite low external humidity. Pyroglutamic acid applied topically to the skin has a temporary moisturising effect, but it is easily washed away and gives no long term skin benefit.

The use of certain esters of pyroglutamic acid as auxiliary agents for accelerating absorption of drugs through the skin is described in JA 60-214744 (Nitto Denki Kogyo KK.

Cosmetics containing one or more compounds obtained by the esterification of 2-pyrrolidone-5-carboxylic acid (PCA) and a fatty acid chosen from straight chain higher fatty acids are described in JA 57-185209 (Nisshin Seiyu KK) for contributing to the natural moisturising factor (NMF) present in the horny layer of the skin, part of which NMF is characterised as a salt of PCA.

Certain esters of pyroglutamic acid described in EP-A-0 176 217 (Unilever) are stated to be analogues of naturally occuring N-terminal pyroglutamic peptides. These naturally occurring peptides are substrates for the enzyme pyroglutamic acid peptidase which represent one route of pyroglutamic acid synthesis in the stratum corneum: [See: J G Barrett and I R Scott (1983), "Pyrrolidone carboxylic acid synthesis in guinea pig epidermis", J Invest. Dermatol. 81, 122].

These esters are stated to readily penetrate into the stratum corneum, and there provide a substrate for this enzyme at the normal site of pyroglutamic acid synthesis, that is, inside the cells of the stratum corneum.

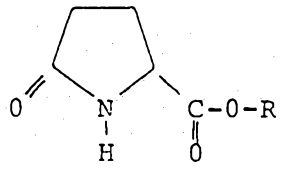
There are, however, certain disadvantages in employing products based on these prior proposals; these are firstly, in aqueous systems, there is a tendency for hydrolysis of the ester of pyroglutamic acid to occur prematurely, so that the free acid, pyroglutamic acid, is present in the composition, and its benefit prior to application to the skin is thereby at best relatively short lived, and secondly, that the presence of drugs in topical products can severely limit their cosmetic usefulness.

We have now discovered that the stability of esters of pyroglutamic acid can be significantly improved and the general cosmetic use widened, by formulating them in an aqueous composition having an acid pH, preferably one which otherwise contains no molecule that could be classed as a drug, thereby limiting its cosmetic usefulness. Also, we have found that the ester of pyroglutamic acid penetrates more readily into the stratum corneum than does the free acid, the penetrated ester being enzymically cleaved, as already stated, to yield pyroglutamic acid in situ in the stratum corneum, thereby to augment that which occurs naturally in this region of the skin. Evidence to support this observation is given later in this specification.

DEFINITION OF THE INVENTION

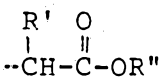
Accordingly, the invention provides an aqueous composition for topical application to human skin which comprises:

(i) from 0.01 to 99% by weight of an ester of pyroglutamic acid having the structure:



(1)

where R is a linear or branched chain saturated or unsaturated ~~alcohol~~ alkyl group having from 1 to 12 atoms,

or the group: 

where R' and R" are the same or different and are each represented by H or the group:

$[(CH_3)_u,(CH_2OH)_v,(CH_2)_w,(CHCH_3)_x,(CHOH)_y,(CH=CH)_z]$ - (2)

where either u or v is 1 and the other of them is zero
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4
y is zero, or an integer of from 1 to 2
z is zero, or an integer of from 1 to 4; and
u + v + w + x + y + z is an integer of from 1 to 22;

the subgroups within the group (2) being in any sequence; provided that when the subgroup (CH=CH) is present, then the total number of carbon atoms in said group (2) will be from 10 to 20; and

(ii) from 1 to 99.99% by weight of a cosmetically acceptable aqueous buffer having an effective pH of from 2 to <7; and

(iii) from 0 to 98.99% by weight of cosmetic adjuncts.

DISCLOSURE OF THE INVENTION

It is accordingly an object of the invention to provide an aqueous composition which is suitable for topical application to human skin, including the lips, mucosae, scalp, and to human hair, comprising certain esters of pyroglutamic acid in an acidic buffer, to provide a source of pyroglutamic acid to the skin, in particular to the stratum corneum, following topical application.

The esters of pyroglutamic acid

Examples of suitable esters of pyroglutamic acid where R in structure (1) is a C_1 to C_{12} linear or branched chain alkyl group are:

pyroglutamic acid methyl ester
pyroglutamic acid ethyl ester
pyroglutamic acid n-propyl ester
pyroglutamic acid n-butyl ester
pyroglutamic acid n-hexyl ester
pyroglutamic acid n-heptyl ester
pyroglutamic acid n-octyl ester
pyroglutamic acid n-nonyl ester
pyroglutamic acid n-decyl ester
pyroglutamic acid n-undecyl ester
pyroglutamic acid n-dodecyl ester
pyroglutamic acid iso-propyl ester
pyroglutamic acid 2-methylhexyl ester
pyroglutamic acid 2-ethylhexyl ester
pyroglutamic acid 3,7-dimethyloctyl ester
pyroglutamic acid 2,4,4-trimethyl-1-pentane ester
pyroglutamic acid methyloctyl ester.

Particularly preferred esters of this group are those where R in structure (1) is C_1 to C_6 alkyl (linear or branched).

Examples of the group (2) include straight and branched chain, saturated or unsaturated aliphatic groups having from 1 to 22 carbon atoms, such as the alkyl groups:

methyl
ethyl
propyl

iso-propyl
butyl
iso-butyl
n-valeryl
iso-valeryl
n-caproyl
n-heptyl
n-caprylyl
n-capryl
lauryl
myristyl
palmityl
stearyl
arachidyl, and
beheryl;

and the C_{10-22} alkenyl groups:

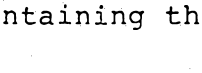
linoleyl
linolenyl
γ-linolenyl
arachidonyl, and
columbinyl.

Examples of the group (2) also include hydroxyalkyl groups having from 1 to 22 carbon atoms, such as:

hydroxymethyl
2-hydroxyethyl
2-hydroxy-n-propyl
3-hydroxy-n-propyl

2-hydroxy-n-butyl
3-hydroxy-n-butyl
4-hydroxy-n-butyl
5-hydroxy-n-valeryl

6-hydroxy-n-caproyl
2,3-dihydroxy-n-propyl
2,3-dihydroxy-n-butyl
12-hydroxystearyl.

Further specific examples of esters of pyroglutamic acid containing the group:  are:

2-[pyroglutamoyloxy]-propionic acid
methyl-2-[pyroglutamoyloxy]-acetate
ethyl-2-[pyroglutamoyloxy]-n-propionate
ethyl-2-[pyroglutamoyloxy]-n-butyrate
ethyl-2-[pyroglutamoyloxy]-iso-butyrate
ethyl-2-[pyroglutamoyloxy]-n-valerate
ethyl-2-[pyroglutamoyloxy]-n-caproate
ethyl-2-[pyroglutamoyloxy]-n-heptylate
ethyl-2-[pyroglutamoyloxy]-n-caprylate
ethyl-2-[pyroglutamoyloxy]-n-pelargonate
ethyl-2-[pyroglutamoyloxy]-3-hydroxybutyrate
iso-propyl-2-[pyroglutamoyloxy]-n-propionate
iso-propyl-2-[pyroglutamoyloxy]-n-caprylate
n-propyl-2-[pyroglutamoyloxy]-n-propionate
n-propyl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-propionate
12-hydroxystearyl-2-[pyroglutamoyloxy]-n-propionate
stearyl-2-[pyroglutamoyloxy]-n-stearate
palmityl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-caprylate

lauryl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-caprylate
glyceryl mono(2-[pyroglutamoyloxy]-n-propionate)
glyceryl mono(2-[pyroglutamoyloxy]-n-caprylate), and
glyceryl di(2-[pyroglutamoyloxy]-n-propionate).

It is to be understood that the above list of specific examples of esters of pyroglutamic acid are not exhaustive, there being many other examples expressed by the generic structure of these esters.

The amount of the esters of pyroglutamic acid or mixtures thereof to be employed in accordance with the invention, will normally be from 0.01 to 99%, preferably from 0.1 to 20% and most preferably from 0.2 to 2% by weight of the composition.

The aqueous buffer

The composition also comprises a cosmetically acceptable aqueous buffer having an effective pH of from 2 to < 7. Accordingly, the composition of the invention will acquire an acid pH determine by this buffer.

As has been stated earlier the stability of the ester of pyroglutamic acid during storage prior to use is enhanced in compositions having an acid pH, as compared with those having a neutral or alkaline pH, where some hyrolysis and premature release of free pyroglutamic acid can occur. Evidence in support of establishing a pH value of <7 is given later in this specification.

Examples of suitable aqueous buffers include:

Citric acid - sodium citrate buffer having a pH of 4.0
Lactic acid - sodium lactate buffer having a pH of 4.0
Acetic acid -sodium acetate buffer having a pH of 4.0

Further details of the formulations of these buffers are given in the Examples.

It is to be understood that the forgoing buffers are only examples of suitable buffers and as such this does not represent an exhaustive list. Other buffers are available and suitable for using in accordance with the invention.

~~Other~~ Vehicles

The composition according to the invention can also optionally comprises a solid, semi-solid or liquid cosmetically and/or physiologically acceptable vehicle, in addition to the buffer, to enable the ester to be conveyed to the skin or hair at an appropriate dilution. The nature of the vehicle will depend upon the method chosen for topical administration of the composition. The vehicle can itself be inert or it can possess physiological or pharmaceutical benefits of its own.

The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition. Suitable vehicles can be classified as described hereinafter.

It should be explained that vehicles are substances which can act as diluents, dispersants, or solvents for the esters which therefore ensure that they can be applied to and distributed evenly over the skin or hair at an appropriate concentration. The vehicle is preferably one which can aid penetration of the ester into the skin to reach the stratum corneum.

Vehicles that can be used in compositions according to the invention can include water and other liquids such as emollients and solvents, and also humectants and thickeners. Examples of each of these types of vehicles, which can be used singly or as mixtures of one or more vehicles, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, ispropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polythylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, sunflower seed oil, evening primrose oil, castor oil, lanolin alcohols, petrolatum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

Propellants, such as trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, monochlorodifluoromethane, trichlorotrifluoroethane, propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol

monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran;

Humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin;

Gelling agents such as soaps and fatty alcohols;

The amount of (optional) vehicle in the composition, can comprise the balance of the composition, particularly where little or no other ingredients are present in the composition. Accordingly, the vehicle or vehicles can comprise preferably from 50 and ideally from 90 to 98.99% by weight of the composition.

Perfume

The composition according to the invention can also optionally comprise a perfume in an amount sufficient to make the composition acceptable to the consumer and pleasant to use. Usually, the perfume when present will form from 0.01 to 10% by weight of the composition.

Activity Enhancer

The composition according to the invention can also optionally comprise an activity enhancer, which can also function as a vehicle, and which can be chosen from a wide variety of molecules that can function in different ways to enhance delivery to the stratum corneum, of the ester or to potentiate its activity. Particular classes of activity enhancers include penetration enhancers and cationic polymers.

Penetration Enhancers

As has been stated earlier, the presence of a penetration enhancer can potentiate the benefit of the ester of pyroglutamic acid, by improving its delivery to the stratum corneum.

The penetration enhancer can accordingly function in a variety of ways. It can for example, improve the distribution of the ester on the skin surface or, it can increase its partition into the skin from the composition when applied topically, so aiding its passage to its site of action. Other mechanisms enhancing the benefit of the chemical inhibitor may also be involved.

Examples of penetration enhancers include:

2-methyl propan-2-ol
Propan-2-ol
Ethyl-2-hydroxypropanoate
Hexan-2,5-diol
POE(2) ethyl ether
Di(2-hydroxypropyl) ether
Pentan-2,4-diol
Acetone
POE(2) methyl ether
2-hydroxypropionic acid
2-hydroxyoctanoic acid
Propan-1-ol
1,4 Dioxane
Tetrahydrofuran

Butan-1,4-diol
Propylene glycol dipelargonate
Polyoxypropylene 15 stearyl ether
Octyl alcohol
POE ester of oleyl alcohol
Oleyl alcohol
Lauryl alcohol
Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate
Dibutyl suberate
Dioctyl azelate
Debenzyl sebacate
Dibutyl phthalate
Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate
Benzyl benzoate

Butyl benzoate
Hexyl laurate
Ethyl caprate
Ethyl caprylate
Butyl stearate
Benzyl salicylate
2-hydroxypropanoic acid
2-hyroxyoctanoic acid,

Further examples of penetration enhancers include:-

Dimethyl sulphoxide
N,N-Dimethyl acetamide
N,N-Dimethyl formamide
2-Pyrrolidone
1-Methyl-2-pyrrolidone
5-Methyl-2-pyrrolidone
1,5-Dimethyl-2-pyrrolidone
1-Ethyl-2-pyrrolidone
Phosphine oxides
Sugar esters
Tetrahydrofurfural alcohol
Urea
Diethyl-m-toluamide, and
1-Dodecylazacycloheptan-2-one

Further examples of penetration enhancers include surface active agents, preferred examples of which include:

(i) Anionic surface active agents, such as metallic or alkanolamine salts of fatty acids for example sodium laurate and triethanolamine oleate;

alkyl benzene sulphonates, for example triethanolamine dodecyl benzene sulphonate;

alkyl sulphates, for example sodium lauryl sulphate;

alkyl ether sulphates, for example sodium lauryl ether sulphate [2 to 8 EO];

sulphosuccinates, for example sodium dioctyl sulphonsuccinate;

monoglyceride sulphates, for example sodium glyceryl monostearate monosulphate;

isethionates, for example sodium isethionate;

methyl taurides, for example Igepon T;

acylsarcosinates, for example sodium myristyl sarcosinate;

acyl peptides, for example Maypons and Lamepons;
acyl lactylates,

polyalkoxylated ether glycollates, for example trideceth-7 carboxylic acid;

phosphates, for example sodium dilauryl phosphate.

(ii) Cationic surface active agents, such as amine salts, for example sapamin hydrochloride;

quartenary ammonium salts, for example Quaternium 5, Quaternium 31 and Quaternium 18;

(iii) Amphoteric suface active agents, such as imidazol compounds, for example Miranol;

N-alkyl amino acids, such as sodium cocaminopropionate and asparagine derivatives;

betaines, for example cocoamidopropylbetaine

(iv) Nonionic surface active agents, such as fatty acid alkanolamides, for example oleic ethanolamide;

esters of polyalcohols, for example Span;

polyglycerol esters, for example that esterified with C_{12-18} fatty acids and one or several OH groups;

polyalkoxylated derivatives, for example polyoxy:polyoxyethylene stearate, and octylphenoxy polyethoxyethanol (TRITON X-100); ethers, for example polyoxyethylene lauryl ether;

ester ethers, for example Tween;

amine oxides, for example coconut and dodecyl dimethyl amine oxides.

Mixtures of two or more of the above surface active agents can be employed in the composition according to the invention.

(c) cationic polymers chosen from:

Guar Hydroxypropyltrimonium chloride
Quaternium-19
Quaternium-23
Quaternium-40
Quaternium-57
Poly(dipropyldiallylammonium chloride)
Poly(methyl-β-propaniodiallylammonium chloride)
Poly(diallylpiperidinium chloride)
Poly(vinyl pyridinium chloride)
Quaternised poly (vinyl alcohol)
Quaternised poly (dimethylaminoethylmethacrylate); and
mixtures thereof.

The amount of activity enhancer, when employed in accordance with the invention, will normally be from 0.1 to 50%, preferably from 0.5 to 25% and most preferably from 0.5 to 10% by weight of the composition.

FURTHER OPTIONAL INGREDIENTS

The composition according to the invention can also optionally contain further ingredients in addition to those which are conventionally used for the provision of the cosmetically - acceptable vehicle.

Accordingly, in addition to ingredients conventionally used in preparing a lotion, cream, ointment, gel, powder, solid stick and aerosol concentrate, the composition can optionally comprise further ingredients such as a colourant, preservative, antioxidant, emollient or aerosol propellant, in amounts which are conventional in the cosmetics or pharmaceutical art.

PREPARATION OF THE COMPOSITION

The composition of the invention can be prepared in the form of a solution, lotion, gel, cream, ointment, solid stick or aerosol, or in any other form suited to administration topically to human skin.

When the composition is a liquid, such as a lotion or aerosol, or a semi-liquid such as a gel, cream or ointment, or a solid stick, then it is usually necessary to dissolve an effective quantity of the ester of pyroglutamic acid, or a mixture thereof, in water or ethanol or other aqueous or non-aqueous cosmetically acceptable vehicle, and then to admix this solution, if desired, in a conventional manner with a suitable cream or ointment base containing, for example an oil or silicone oil and water, or stick base containing a gelling agent such as sodium stearate, or with a normally liquefiable gaseous propellant in order to prepare the composition.

If desired, other cosmetically acceptable carriers, diluents or emollients can be incorporated in the therapeutic composition according to the invention, in order to facilitate even distribution over the skin or hair at a suitable concentration

Evidence to support requirement of acid pH value for improved stability of the ester of pyroglutamic acid

As has been stated earlier, the stability of the ester of pyroglutamic acid during storage prior to use is enhanced in compositions having an acid pH, compared with those having a neutral or alkaline pH. It is accordingly apparent that hydrolysis of the ester with premature release of free pyroglutamic acid can occur faster at higher pH values than at lower values. Compositions having maximum skin benefit are therefore those having a pH value of <7 containing the unchanged ester of pyroglutamic acid with minimal free pyroglutamic acid.

In order to demonstrate the effect of pH on the stability of esters of pyroglutamic acid, the half-life of selected esters at selected pH values was measured as follows:

i) The chosen ester of pyroglutamic acid was dissolved in aqueous buffer of a selected pH value, to provide a 0.1% w/v solution of the ester;

ii) Intact (unhydrolysed) ester was analysed by high performance liquid chromatography at regular time intervals.

iii) The log of the amount of the ester remaining intact versus time was plotted to give a straight line response.

iv) From this plot, the time required for half of the ester of pyroglutamic acid to be hydrolysed (half of the ester remaining intact), can be determined if necessary by extrapolation.

Using this method, the half-life of selected esters of pyroglutamic acid was determined and the results obtained were as follows:

Table 1

STABILITY OF VARIOUS ALKYL ESTERS OF PYROGLUTAMIC ACID*

	HALF LIFE IN HOURS	
ESTER	pH 7.0	pH 4.0
Ethyl-2-[pyroglutamoyloxy]-n-propionate	9	1,700
Pyroglutamic acid ethyl ester	58	11,000
Pyroglutamic acid n-butyl ester	80	15,000
Pyroglutamic acid n-hexyl ester	96	18,000
Pyroglutamic acid n-octyl ester	96	18,000

* Assay performed in 100mM phosphate buffer at 30°C.

The half-life of pyroglutamic acid ethyl ester was also determined over a narrower range of pH values on either side of neutrality to illustrate the importance of selecting a pH value for improved stability of <7.

Table 2

STABILITY OF PYROGLUTAMIC ACID ETHYL ESTER AT pH VALUES NEAR NEUTALITY

pH value	Half-life (days)
6.5	12
6.8	7
7.0	2.4
7.4	2
7.8	1

The above results in Tables 1 and 2 indicate that there is a rapid fall-off in stability of esters of pyroglutamic acid with increasing pH value. Ideally, compositions according to the invention should be shelf stable for at least one year, which involves selection of a suitable pH value to enable the chosen esters of pyroglutamic acid to have a half-life of at least one year.

Evidence to support benefit of topical application to skin of the ester of pyroglutamic acid versus the free acid

When pyroglutamic acid is applied topically to human skin, only a negligible amount is able to penetrate to the stratum corneum to augment that naturally present in this region of the skin. However, certain esters of pyroglutamic acid are able readily to penetrate the skin to reach the stratum corneum, where naturally occuring esterases cleave the ester to yield the free pyroglutamic acid which can then augment that which is naturally present in the skin, with the consequence that skin benefit is improved.

Delivery of esters of pyroglutamic acid, with subsequent hydrolysis to yield free pyroglutamic acid in the stratum corneum, was confirmed using tritiated esters of pyroglutamic acid and a radio-tracer technique.

Accordingly, [^{3}H] esters of pyroglutamic acid were each dissolved at 1% w/v in anhydrous ethanol or in an oil-in-water emulsion base. These solutions were then applied to the arms of volunteers, left for 18 hours, washed with soap and water, and the stratum corneum was removed by stripping with Sellotape. The [^{3}H] pyroglutamic acid was separated from unchanged ester by chromotography on AG1X8 resin and the amount delivered to the skin expressed as nmoles per mg of stratum corneum protein.

The result obtained are summarised in Table 3:

Table 3

Ester of Pyroglutamic acid	Pyroglutamic acid delivered (n mol/mg protein)	
	Ethanol base	Cream base
Ethyl	8	5
Butyl	6	2
Hexyl	5	2
Octyl	4	1
Dodecyl	4	1

When [^{3}H] pyroglutamic acid instead of a corresponding ester was applied topically in this experiment, a negligible amount of the tritiated free acid was recovered from the stratum corneum.

The above results (Table 3) indicate that pyroglutamic acid is effectively delivered to the stratum corneum following topical application of an ester thereof, while little pyroglutamic acid reached the stratum corneum if applied as the free acid. These results also indicate a preference for short alkyl chain esters, since the shorter the alkyl chain of the ester, the more effective is the delivery of the ester to the stratum corneum, as judged by the higher yield of pyroglutamic acid found in that region of the skin.

Examples

The invention is further illustrated by the following examples.

Example 1.

BUFFERED SKIN CARE FORMULATION NO 1.

1. Base Formulation for Buffer

Ingredient	% by wt
triglycerides	31.0
glyceryl stearate	6.0
cetyl alcohol	1.2
stearic acid	2.0
lanolin	4.0
propylene glycol	2.0
preservative	0.3
fragrance	0.4
Pyroglutamic acid ethyl ester	1.0
BUFFER 'A'	qv
deionized water balance to	100.00

pH = 4.0

Buffer 'A' : Citric acid - sodium citrate

Ingredient	% by wt
citric acid	1.38
Na citrate	1.01

pH adjusted to 4.0 with 0.1M citric acid or 0.1M sodium citrate.

Example 2.

BUFFERED SKIN CARE FORMULATION NO 2.

1. Base Formulation for Buffer

Ingredient	% by wt
triglycerides	31.0
glyceryl stearate	6.0
cetyl alcohol	1.2
stearic acid	2.0
lanolin	4.0
propylene glycol	2.0
preservative	0.3
fragrance	0.4
Pyroglutamic acid hexyl ester	3.0
BUFFER 'B'	qv
deionized water balance to	100.00

pH = 4.0

Buffer 'B' : Lactic acid - sodium lactate

Ingredient		% by wt
lactic acid (1M)		0.90 sodium
lactate (1M)	0.75	

pH adjusted to 4.0 with 0.1M lactic acid or 0.1M sodium lactate.

Example 3.

BUFFERED SKIN CARE FORMULATION NO 3.

1. Base Formulation for Buffer

Ingredient		% by wt
triglycerides		31.0
glyceryl stearate		6.0
cetyl alcohol		1.2
stearic acid		2.0
lanolin		4.0
propylene glycol		2.0
preservative		0.3
fragrance		0.4
ethyl -2 [pyroglutamoyloxy]-n-propionate		3.0
BUFFER 'C'		qv
deionized water	balance to	100.00

pH = 4.0

Buffer 'C' : Acetic acid - sodium acetate

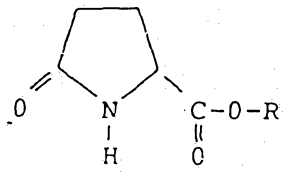
Ingredient	% by wt
acetic acid (1M)	8.2
Sodium acetate	0.25

pH adjusted to 4.0 with 0.1M acetic acid or 0.1M Sodium acetate.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An aqueous composition for topical application to human skin which comprises:

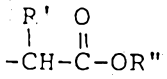
(i) from 0.01 to 99% by weight of an ester of pyroglutamic acid having the structure:



(1)

where R is a linear or branched chain saturated or unsaturated alkyl group having from 1 to 12 atoms,

or the group:



where R' and R" are the same or different and are each represented by H or the group:

$$[(CH_3)_u,(CH_2OH)_v,(CH_2)_w,(CHCH_3)_x,(CHOH)_y,(CH=CH)_z] \quad (2)$$

where either u or v is 1 and the other of them is zero
w is zero, or an integer of from 1 to 21
x is zero, or an integer of from 1 to 4
y is zero, or an integer of from 1 to 2
z is zero, or an integer of from 1 to 4; and
u + v + w + x + y + z is an integer of from 1 to 22;

the subgroups within the group (2) being in any sequence; provided that when the subgroup (CH=CH) is present, then the total number of carbon atoms in said group (2) will be from 10 to 20; and

(ii) from 1 to 99.99% by weight of a cosmetically acceptable aqueous buffer having an effective pH of from 2 to <7; and

(iii) from 0 to 98.99% by weight of cosmetic adjuncts.

2. A composition according to claim 1, in which the ester of pyroglutamic acid is chosen from those where R in Structure (1) is a C_1 to C_{12} linear or branched chain alkyl group.

3. A composition according to claim 1 or 2, in which the ester of pyroglutamic acid is chosen from:

pyroglutamic acid methyl ester
pyroglutamic acid ethyl ester
pyroglutamic acid n-propyl ester
pyroglutamic acid n-butyl ester
pyroglutamic acid n-hexyl ester
pyroglutamic acid n-heptyl ester
pyroglutamic acid n-octyl ester
pyroglutamic acid n-nonyl ester
pyroglutamic acid n-decyl ester
pyroglutamic acid n-undecyl ester
pyroglutamic acid n-dodecyl ester
pyroglutamic acid iso-propyl ester
pyroglutamic acid 2-methylhexyl ester

pyroglutamic acid 2-ethylhexyl ester
pyroglutamic acid 3,7-dimethyloctyl ester
pyroglutamic acid 2,4,4-trimethyl-1-pentane ester
pyroglutamic acid methyloctyl ester.

4. A composition according to claim 1, in which the R group in structure (1) is respresented by group (2).

5. A composition according to claim 4, in which the group (2) is chosen from straight or branched chain, saturated or unsaturated aliphatic groups having from 1 to 22 carbon atoms, or from alkenyl groups having from 10 to 22 carbon atoms.

6. A composition according to claims, 1 4 or 5, in which the ester of pyroglutamic acid is chosen from:

2-[pyroglutamoyloxy]-propionic acid
methyl-2-[pyroglutamoyloxy]-acetate
ethyl-2-[pyroglutamoyloxy]-n-propionate
ethyl-2-[pyroglutamoyloxy]-n-butyrate
ethyl-2-[pyroglutamoyloxy]-iso-butyrate
ethyl-2-[pyroglutamoyloxy]-n-valerate
ethyl-2-[pyroglutamoyloxy]-n-caproate
ethyl-2-[pyroglutamoyloxy]-n-heptylate
ethyl-2-[pyroglutamoyloxy]-n-caprylate
ethyl-2-[pyroglutamoyloxy]-n-pelargonate
ethyl-2-[pyroglutamoyloxy]-3-hydroxybutyrate
iso-propyl-2-[pyroglutamoyloxy]-n-propionate
iso-propyl-2-[pyroglutamoyloxy]-n-caprylate
n-propyl-2-[pyroglutamoyloxy]-n-propionate
n-propyl-2-[pyroglutamoyloxy]-n-caprylate

stearyl-2-[pyroglutamoyloxy]-n-propionate
12-hydroxystearyl-2-[pyroglutamoyloxy]-n-propionate
stearyl-2-[pyroglutamoyloxy]-n-stearate
palmityl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-propionate
linoleyl-2-[pyroglutamoyloxy]-n-caprylate
lauryl-2-[pyroglutamoyloxy]-n-caprylate
stearyl-2-[pyroglutamoyloxy]-n-caprylate
glyceryl mono(2-[pyroglutamoyloxy]-n-propionate)
glyceryl mono(2-[pyroglutamoyloxy]-n-caprylate), and
glyceryl di(2-[pyroglutamoyloxy]-n-propionate).

7. A composition according to any preceding claim, in which the amount of the ester of pyroglutamic acid is from 0.01 to 20% by weight of the composition.

8. A composition according to any preceding claim, in which the buffer is chosen from:

a citric acid - sodium citrate buffer having a pH of 4.0
a lactic acid - sodium lactate buffer having a pH of 4.0, and
an acetic acid - sodium acetate buffer having a pH of 4.0

9. A composition according to any preceding claim which additionally comprises from 0.01 to 10% by weight of a perfume.

10. The composition according to any one of the preceding claims, which further comprises 0.1 to 50% by weight of the composition, of a penetration enhancer, surface active agent or cationic polymer with activity enhancing ability.

DATED THIS 2ND DAY OF DECEMBER 1991
UNILEVER PLC
By its Patent Attorneys:
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