1. Use of a salicylic acid derivative salified with a base, as a dispersing agent of an oily phase in an aqueous phase to obtain an oil-in-water emulsion free of emulsifying agent, said derivative being at the oil-water interface.

9. Cosmetic and/or dermatological emulsion, characterized in that it contains at least one salicylic acid derivative of formula (I) below, salified with a base:

![Chemical Structure](image-url)

in which:

.../2
R represents a saturated, linear, branched or cyclized aliphatic, alkoxy, ester or ketoxy group, or an unsaturated group bearing one or more conjugated or non-conjugated double bonds, these groups containing from 2 to 22 carbon atoms and being able to be substituted with at least one substituent chosen from halogen atoms, the trifluoromethyl group, hydroxyl groups in free form or esterified with an acid having from 1 to 6 carbon atoms or alternatively with a carboxyl function, which is free or esterified with a lower alcohol having from 1 to 6 carbon atoms;

R' represents a hydroxyl group or an ester function of formula:

\[-O-C-R_1\]

where \( R_1 \) is a saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms,
said derivative being at the oil-water interface.
AUSTRALIA
Patents Act 1990

COMPLETE SPECIFICATION
STANDARD PATENT

Applicant:
L'OREAL

Invention Title:
USE OF A SALICYLIC ACID DERIVATIVE AS A STABILIZER FOR AN OIL-IN-WATER EMULSION

The following statement is a full description of this invention, including the best method of performing it known to me/us:
The present invention relates to the use of a salicylic acid derivative as a stabilizer for an oil-in-water emulsion, as well as to cosmetic and/or dermatological emulsions containing this derivative. These emulsions are intended in particular for the treatment or care of the skin, both of the human face and body, including the scalp and the nails, and even more especially for treating and/or combating acne, greasy skin with a tendency towards acne, and the ageing (wrinkles, fine lines, complexion) and pigmentation of the skin.

It is known to use salicylic acid derivatives as keratolytic agents for treating acne and as an anti-ageing agent in cosmetic and/or dermatological compositions (see FR-A-2,581,542 and EP-A-378,936). These derivatives are of great value, given their biological effects on the skin. They make it possible in particular to impart a light and radiant complexion to the face, and thus a healthy look and a smooth and younger appearance, as well as making it possible to remove comedones caused by acne.

However, their use poses a problem insofar as they are in crystalline form and insofar as they are soluble neither in water nor in the oils traditionally used in the cosmetic and dermatological fields, such as mineral oils (petrolatum, paraffin).

Thus, if they are introduced as they are into cosmetic and/or dermatological compositions, they remain in the form of crystals, thereby making the use of the composition containing them inefficient for treating the skin.

On the other hand, these derivatives are soluble in lower alcohols such as ethanol or isopropanol, Guerbet alcohols or in solvents such as octyldecanol, certain glycols, short-chain (< C12) fatty alcohols, which are polyoxyethylenated or polyoxypropylenated, or alternatively short-chain (< C12) esters.

The lower alcohols have the drawback of drying and irritating the skin; they are poorly tolerated by sensitive or fragile skin, especially in repeated applications. It is thus preferred to avoid using them in body- and/or face-care products.

Moreover, the short-chain fatty alcohols and fatty esters, as well as certain glycols, make it
possible to solubilize these derivatives, leading to the deep-down penetration of active agents into the skin, which is not necessarily desirable for care products.

Currently, it is increasingly sought generally to limit the use of solvents in skin-care products, since these solvents are not always well tolerated and may lead to irritation when they are used in too large an amount.

The Applicant has thus sought to formulate the salicylic acid derivatives in compositions containing the least possible amount of solvents.

Moreover, these derivatives have the major drawback of causing stinging, itching and pulling sensations after their application, which may lead to a level of discomfort such that their use by individuals with sensitive skin is often prevented. This discomfort is due in particular to the acidic functional group of these derivatives.

Thus, there is a need for a cosmetic and/or dermatological composition based on a salicylic acid derivative, which imparts this healthy look and rejuvenation to the skin and also removes comedones, without resulting in the above drawbacks.

The Applicant has especially found, surprisingly, that the salicylic acid derivatives could be introduced in salified form into cosmetic and/or dermatological compositions, without these derivatives recrystallizing and without it being necessary to use a large amount of solvent. The Applicant has found, surprisingly, that it was possible to stabilize oil-in-water emulsions with salts of salicylic acid derivatives, making it possible to dispense with the use of irritant lipophilic solvents, without being inconvenienced by recrystallization of these derivatives.

Thus, this or these derivative(s) lie at the oil-water interface and surround the oil droplets and stably stabilize the obtained emulsion without use of emulsifying agent.

More precisely, the subject of the invention is the use of at least one salicylic acid derivative salified with a base, as a dispersing agent of an oily phase in an aqueous phase to obtain an oil-in-water emulsion free of emulsifying agent.
These salified derivatives also have the advantage of being less aggressive than their acidic counterparts, while at the same time having comparable properties.

In particular, the salicylic acid derivatives to which the invention applies have the following formula (I):

![Chemical Structure Image]

in which:

- \( R \) represents a saturated, linear, branched or cyclized aliphatic, alkoxy, ester or ketoxy group, or an unsaturated group bearing one or more conjugated or non-conjugated double bonds, these groups containing from 2 to 22 carbon atoms and being able to be substituted with at least one substituent chosen from halogen atoms, the trifluoromethyl group, hydroxyl groups in free form or esterified with an acid having from 1 to 6 carbon atoms or alternatively with a carboxyl function, which is free or esterified with a lower alcohol having from 1 to 6 carbon atoms;

- \( R' \) represents a hydroxyl group or an ester function of formula:

\[
\begin{align*}
-O-C-R_1 \\
0
\end{align*}
\]

where \( R_1 \) is a saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms.
This emulsion may be used in all the fields using a pharmaceutical form of this type, and especially in the cosmetic and pharmaceutical fields.

Thus, the subject of the invention is also a cosmetic and/or dermatological emulsion containing at least one salified salicylic acid derivative advantageously having the above formula (I) said derivative being at the oil-water interface.

The radical R preferably contains at least 4 carbon atoms. It is formed, for example, of a saturated linear alkyl or alkoxy radical having from 4 to 11 carbon atoms.

The salicylic acid derivative is advantageously chosen from n-octanoyl-5-salicylic acid, n-decanoyl-5-salicylic acid, n-dodecanoyl-5-salicylic acid, n-octyl-5-salicylic acid, n-heptyloxy-5-salicylic acid and n-heptyloxy-4-salicylic acid, which are salified with a base. It is possible, however, to use the salts of 5-tert-octylsalicylic acid, 3-tert-butyl-5- or 6-methylsalicylic acid, 3,5-diisopropylsalicylic acid, 5-butoxysalicylic acid or 5-octyloxysalicylic acid. It is also possible to use those described in document EP-A-570,230.

As a base capable of salifying the salicylic acid derivative, there may be mentioned inorganic bases such as alkali metal hydroxides (sodium hydroxide and potassium hydroxide) or ammonium hydroxides, or better still organic bases.

Contrary to the teaching of Patent US-A-5,091,171, the Applicant has found that the salified salicylic acid derivatives had properties comparable to those of the corresponding acidic salicylic acid derivative, irrespective of the base used for the salification (including the alkali metal hydroxides).

Amphoteric bases are preferably used for the salification of the salicylic acid derivatives, that is to say bases having both anionic and cationic functional groups.

The amphoteric bases may be primary, secondary, tertiary or cyclic organic amines and more especially amino acids. Examples of amphoteric bases which may be mentioned are glycine, lysine, arginine, taurine, histidine, alanine, valine, cysteine, trihydroxymethylaminomethane (TRISTA) and
triethanolamine. These bases are used in amounts sufficient to bring the pH of the emulsion to between 5 and 7, and thus close to the pH of the skin. This results in great compatibility between the emulsion of the invention and the skin.

The base is preferably arginine or, better still, lysine. The latter makes it possible to obtain a very fine emulsion which is stable for at least 2 months at room temperature.

As examples of a salified salicylic acid derivative which may be used in the invention, there may be mentioned N,N-dimethyl-N-(2-hydroxyethyl)ammonium 5-n-dodecanoylsalicylate, abbreviated to DHADS, hexadecyltrimethylammonium 5-n-octanoylsalicylate and, generally, all the amino derivatives cited in document FR-A-2,607,498. It is also possible to use those described in document EP-A-36,534.

According to the invention, the salified salicylic acid derivative or derivatives may be used in an amount sufficient to ensure stabilization of the oil as well as its dispersion in the aqueous phase. In practice, from 0.1% to 10% by weight of derivative is used relative to the total weight of emulsion, and preferably from 1% to 5%.

The emulsions of the invention may contain one or more oils conventionally used in the cosmetic and dermatological fields. In particular, it is possible to use a plant oil (sunflower oil, sweet almond oil, blackcurrant pip oil or apricot oil), a mineral oil (petrolatum), a silicone-containing oil (cyclomethicone containing 5 or 6 Si-O groups) or a fluoro oil (perfluoropolyether).

One or more polar oils are advantageously used and, for example, an oil chosen from miglyol and synthetic oils (purcellin oil, fatty alcohols, esters or acids such as triglycerides, octyl palmitate or myristate, and hydroxylated, oxyethyleneated or oxypropylenated esters or ethers such as isostearyl or myristyl lactate).

The oil or oils of the invention may be used in a proportion of from 10% to 70% of the total weight of the emulsion, and preferably from 20% to 40%.

It is possible to introduce into the emulsion of the invention one or more other constituents.
conventionally used in the fields considered, such as antioxidants (vitamin E), preserving agents, opacifying agents, dyes, pigments (titanium oxide or zinc oxide), fragrances, fillers and also lipophilic adjuvants such as essential oils or essential fatty acids, ceramides, pseudoceramides and glyceroceramides. These adjuvants may represent, in total, from 0.1% to 15% of the total weight of the emulsion.

The emulsion of the invention may also contain one or more gelling agents such as clays, polysaccharide gums (xanthan), carboxyvinyl polymers or carbomers. These gelling agents are preferably used at concentrations ranging from 0.1% to 10% of the total weight of the composition.

The emulsion of the invention may also contain one or more lipophilic or hydrophilic active agents other than the salified salicylic acid derivatives used as stabilizer for the emulsion. These active agents may be moisturizing and/or cicatrizing agents (glycerol and allantoin and the derivatives thereof and compositions containing them), β-hydroxy acids and especially salicylic acid and the non-salified derivatives thereof, α-hydroxy acids such as glycolic acid, tartaric acid, etc., hydrophilic or lipophilic screening agents for screening visible and/or ultraviolet rays, as well as dermatological active agents. These active agents are employed in the amounts conventionally used in the fields considered, and especially in a proportion of from 0.05% to 5% of the total weight of the emulsion.

Advantageously, the emulsions of the invention are free of solvent and/or free of emulsifying agent. This also acts in favour of a quite unaggressive and non-irritant emulsion which is capable of being used by individuals with sensitive skin.

A further subject of the invention is the use of the above emulsion for the non-therapeutic treatment of the skin, by topical application.

Another subject of the invention is the use of the above emulsion in order to prevent and/or combat acne and/or greasy skins and/or the ageing and/or pigmentation of the skin, in a non-therapeutic manner.

A further subject of the invention is a process for the cosmetic treatment of the skin in order to combat acne and/or greasy skins and/or the ageing
and/or pigmentation of the skin, which consists in applying the emulsion defined above to the skin. The description which follows is given as an illustration and with no limitation being implied. In the examples, the percentage is given by weight.

**Example 1**

- n-Octanoyl-5-salicylic acid 5%
- Lysine 1 molar equivalent
- Miglyol 812 70%
- Preserving agents 0.3%
- Deionized water qs 100%

This emulsion is fairly compact and has a slightly greasy feel. It is in the form of an ointment for treating very dry skin.

**Example 2: Anti-ageing cream for the face**

- n-Octanoyl-5-salicylic acid 1.5%
- Lysine 1.6%
- Plant oil 22%
- Glyceryl behenate (fatty substance) 1%
- Purcellin oil 2%
- Liquid fraction of karite butter 3%
- Cyclomethicone D5 5%
- Xanthan gum 0.3%
- Glycerol 3%
- Preserving agents 0.7%
- Antioxidant 0.05%
- Deionized water qs 100%

By applying this light cream to the face daily, the fine wrinkles fade, the complexion becomes shiny and the skin is made smoother during the treatment.

**Example 3: Anti-ageing cream for the body**

- n-Octanoyl-5-salicylic acid 2.5%
- Lysine 2.13%
- Miglyol 812 35%
- Carbomer 0.75%
- Preserving agents 0.3%
- Deionized water qs 100%
When applied daily to the body, this soft cream has lightening and smoothing effects on the skin, which is made very soft by the treatment.

5 **Example 4: Anti-ageing cream for the face**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Octanoyl-5-salicylic acid</td>
<td>1%</td>
</tr>
<tr>
<td>Lysine</td>
<td>1.3%</td>
</tr>
<tr>
<td>N-oleylidihydrophingosine</td>
<td>0.1%</td>
</tr>
<tr>
<td>Apricot almond oil</td>
<td>20%</td>
</tr>
<tr>
<td>Liquid fraction of karite butter</td>
<td>8%</td>
</tr>
<tr>
<td>Mixture of cetylstearyl 2-ethylhexanoate and isopropyl myristate (90/10) (fatty substance)</td>
<td>4%</td>
</tr>
<tr>
<td>Preserving agents</td>
<td>0.6%</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.05%</td>
</tr>
<tr>
<td>Carbomer</td>
<td>0.75%</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.3%</td>
</tr>
<tr>
<td>Glycerol</td>
<td>5%</td>
</tr>
<tr>
<td>Mixture of fatty alcohols</td>
<td></td>
</tr>
<tr>
<td>(Stearyl/octyldodecanol/behenyl 40/10/50)</td>
<td>1%</td>
</tr>
<tr>
<td>Deionized water</td>
<td>qs</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>

The Applicant tested the emulsion of Example 4 according to the invention, for the ageing treatment on a panel of 10 women. The emulsion of Example 4 was considered to be as effective as an emulsion containing non-salified n-octanoyl-5-salicylic acid, all factors being otherwise equal, with, in addition, an absence of irritation.

Moreover, the Applicant tested the desquamation caused by the emulsion of Example 4, in comparison with the same formula containing no lysine, using a paddle turbomixer.

The paddle turbomixer makes it possible to measure the spontaneous desquamation. This turbomixer comprises a chamber, and a paddle placed in this chamber. The turbomixer is placed on the sampling surface, for example the arm of the test individual, such that the paddle does not touch this surface; 0.3 ml of a phosphate buffer is introduced into the chamber of the turbomixer, and the paddle is rotated for 1 min., which stirs the phosphate buffer.

The keratinocytes ready to desquamate detach spontaneously from the skin and end up in the phosphate
buffer. The buffer containing the corneocytes thus removed is then collected in a glass tube and the tube is centrifuged for 10 min. at 4,000 rpm. The supernatant is drawn off so as to keep only 1 ml of suspension. The corneocytes are stained (stain = 1 volume of 1% basic fuschin + 1 volume of 1% crystal violet) and are counted under a microscope. The number of corneocytes counted is greater the more the product applied beforehand to the sampling surface promotes desquamation.

The test is performed at $T_0$ and $T_{24h}$, that is to say at the time of application of the cream and 24 hours after application.

The result of the test given below shows that the emulsion of Example 4 results in better desquamation than that of the lysine-free emulsion, and thus has a greater keratolytic effect.

<table>
<thead>
<tr>
<th></th>
<th>$T_0$</th>
<th>$T_{24h}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion of Example 4</td>
<td>63.5</td>
<td>173.6</td>
</tr>
<tr>
<td>Lysine-free emulsion</td>
<td>60.9</td>
<td>67.5</td>
</tr>
<tr>
<td>Naked skin</td>
<td>67.5</td>
<td>66.5</td>
</tr>
</tbody>
</table>

The table below shows the effect of the dose of emulsifying agent of the invention on the stability of the emulsion. The composition studied is as follows:

- n-Octanoyl-5-salicylic acid: $x\%$
- Lysine: $y\%$
- Miglyol 812: 34.85%
- Carbomer: 0.75%
- Preserving agents: 0.7%
Deionized water qs 100%

y = 1 molar equivalent in order to salify x + that required to neutralize the carbomer.

<table>
<thead>
<tr>
<th>Dose x</th>
<th>Dose y</th>
<th>Result (T₀)</th>
<th>Viscosity (T₀)</th>
<th>pH (T₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>0.8</td>
<td>breaks after 1/4 hour</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.5</td>
<td>1.03</td>
<td>fine-some release of oil close to the edges</td>
<td>72 poises</td>
<td>5.89</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
<td>very fine</td>
<td>40 poises</td>
<td>6.07</td>
</tr>
<tr>
<td>1.5</td>
<td>1.58</td>
<td>very fine</td>
<td>36 poises</td>
<td>5.82</td>
</tr>
<tr>
<td>2.5</td>
<td>2.13</td>
<td>very fine</td>
<td>20 poises</td>
<td>5.83</td>
</tr>
<tr>
<td>5</td>
<td>3.51</td>
<td>very fine - no recrystallization at T₁₅</td>
<td>8.6 poises</td>
<td>5.78</td>
</tr>
</tbody>
</table>

The expression very fine is understood to refer to an emulsion having 0.3 μm to 0.5 μm oil droplets.

From this table, it is observed that the emulsion is stable, is free of n-octanoyl-5-salicylic
acid crystals, and has fine, or even very fine, oil
droplets dispersed in water for amounts of salicylic
acid derivative ranging from 0.1% to 0.5% by weight, at
the initial time \( T_0 \). For a stability of several days, it
is desirable to use from 1% to 5% by weight of
salicylic acid derivative as emulsifying agent.

The Applicant has thus indeed found an
effective means of stabilizing salicylic acid
derivatives, while at the same time removing the
irritant side effects of the compositions of the prior
art containing these derivatives in acid form. Thus, it
is now possible for individuals with sensitive skin to
use compositions containing these derivatives in order
to combat and/or prevent acne, greasy skin, and the
ageing and pigmentation of the skin.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of a salicylic acid derivative salified with a base, as a dispersing agent of an oily phase in an aqueous phase to obtain an oil-in-water emulsion free of emulsifying agent, said derivative being at the oil-water interface.

2. Use according to Claim 1, characterized in that the derivative has the following formula (I):

\[
\begin{align*}
\text{O} & \quad \text{C} & \quad \text{H} \\
\text{R} & \quad \text{R'} & \quad \text{(I)} \\
\end{align*}
\]

in which:

- R represents a saturated, linear, branched or cyclized aliphatic, alkoxy, ester or ketoxy group, or an unsaturated group bearing one or more conjugated or non-conjugated double bonds, these groups containing from 2 to 22 carbon atoms and being able to be substituted with at least substituent chosen from
halogen atoms, the trifluoromethyl group, hydroxyl
groups in free form or esterified with an acid having
from 1 to 6 carbon atoms or alternatively with a
carboxyl function, which is free or esterified with a
lower alcohol having from 1 to 6 carbon atoms;
R' represents a hydroxyl group or an ester
function of formula:
\[
\begin{array}{c}
\text{O-C-R}_1 \\
\text{O}
\end{array}
\]

where R$_1$ is a saturated or unsaturated aliphatic group
having from 1 to 18 carbon atoms.

3. Use according to Claim 2, characterized in
that the radical R is an alkyl or alkoxy radical having
from 4 to 11 carbon atoms.

4. Use according to any one of the preceding
claims, characterized in that the salicylic acid
derivative is n-octanoyl-5-salicylic acid.

5. Use according to any one of the preceding
claims, characterized in that the base is an organic
base.
6. Use according to any one of the preceding claims, characterized in that the base is an amphoteric base.

7. Use according to any one of the preceding claims, characterized in that the base is chosen from amino acids.

8. Use according to any one of the preceding claims, characterized in that the base is chosen from arginine and lysine.

9. Cosmetic and/or dermatological emulsion, characterized in that it contains at least one salicylic acid derivative of formula (I) below, salified with a base:

\[ \text{(I)} \]

in which:
R represents a saturated, linear, branched or cyclized aliphatic, alkoxy, ester or ketoxy group, or an unsaturated group bearing one or more conjugated or non-conjugated double bonds, these groups containing from 2 to 22 carbon atoms and being able to be substituted with at least one substituent chosen from halogen atoms, the trifluoromethyl group, hydroxyl groups in free form or esterified with an acid having from 1 to 6 carbon atoms or alternatively with a carboxyl function, which is free or esterified with a lower alcohol having from 1 to 6 carbon atoms;

R' represents a hydroxyl group or an ester function of formula:

\[
\begin{array}{c}
\text{O} \\
\text{O-C-R}_1
\end{array}
\]

where \(R_1\) is a saturated or unsaturated aliphatic group having from 1 to 18 carbon atoms, said derivative being at the oil-water interface.

10. Emulsion according to Claim 9, characterized in that it is free of emulsifying agent.
11. Emulsion according to Claim 9 or 10, characterized in that the radical R is an alkyl or alkoxy radical having from 4 to 11 carbon atoms.

12. Emulsion according to one of Claims 9 to 11, characterized in that the salicylic acid derivative is n-octanoyl-5-salicylic acid.

13. Emulsion according to one of Claims 9 to 12, characterized in that the base is an organic base.

14. Emulsion according to any one of Claims 9 to 13, characterized in that the base is an amphoteric base.

15. Emulsion according to any one of Claims 9 to 14, characterized in that the base is chosen from amino acids.

16. Emulsion according to any one of Claims 9 to 15, characterized in that the base is chosen from arginine and lysine.

17. Emulsion according to any one of Claims 9 to 16, characterized in that the derivative represents from 0.5% to 10% of the total weight of the emulsion.
18. Emulsion according to any one of Claims 9 to 17, characterized in that it contains at least one polar oil.

19. Emulsion according to Claim 18, characterized in that the oil represents from 10% to 70% of the total weight of the emulsion.

20. Emulsion according to any one of Claims 9 to 19, characterized in that it also contains an adjuvant chosen from ceramides, pseudoceramides, glycoceramides and essential fatty acids.

21. Emulsion according to any one of Claims 9 to 20, characterized in that it contains, in addition, at least one gelling agent.

22. Use of the emulsion according to any one of Claims 9 to 21, for the non-therapeutic treatment of the skin.

23. Use of the emulsion according to any one of Claims 9 to 21, for preventing and/or combating acne and/or greasy skin and/or the ageing and/or pigmentation of the skin, in a non-therapeutic manner.

24. Cosmetic treatment process for the skin in order to combat acne and/or greasy skin and/or the ageing and/or pigmentation of the skin, which consists
in applying the emulsion according to any one of Claims

9 to 21 to the skin.

DATED THIS 12TH DAY OF OCTOBER 1995

L'OREAL
By its Patent Attorneys:
GRIFFITH HACK & CO.

Fellows Institute of Patent
Attorneys of Australia
ABSTRACT

USE OF A SALICYLIC ACID DERIVATIVE AS A STABILIZER FOR AN OIL-IN-WATER EMULSION

The invention relates to the use of a salicylic acid derivative salified with a base, as a stabilizer for an oil-in-water emulsion. This derivative has the same properties as its acidic homologue, while at the same time having a less irritant nature. This derivative is, in particular, an n-alkanoyl-5-salicylic acid salified with an amphoteric base such as lysine or arginine. This composition is more especially intended for the cosmetic and dermatological fields.