(54) Titre : INHIBITION DE L'ADHESION DE MICRO-ORGANISMES PATHOGENES PAR UN SUCROSE STEARATE ET/OU DE SORBITAN DANS LE TRAITEMENT COSMETIQUE DE L'ATOPIE CUTANEE

(54) Title: INHIBITION OF THE ADHESION OF PATHOGENIC MICROORGANISMS BY A SUCROSE STEARATE AND/OR A SORBITAN ESTER IN THE COSMETIC TREATMENT OF CUTANEOUS ATOPY

(57) Abrégé/Abstract:
A composition for topical application comprising: -at least one sucrose stearate comprising at least 70% by weight of monoesters of sucrose and of stearic acid, the rest being composed of diesters, triesters and polyesters of sucrose and of stearic acid, -and/or a sorbitan ester, for use in the therapeutic treatment of cutaneous atopy, as an agent for inhibiting the adhesion of Staphylococcus aureus to human nasal mucosa and skin.
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(54) Title : INHIBITION OF THE ADHESION OF PATHOGENIC MICROORGANISMS BY A SUCROSE STEARATE AND/OR A SORBITAN ESTER IN THE COSMETIC TREATMENT OF CUTANEOUS ATOPY

(54) Titre : INHIBITION DE L'ADHÉSION DES MICRO-ORGANISMES PATHOGENES PAR UN SUCROSE STEARATE ET/OU DE SORBITAN DANS LE TRAITEMENT COSMÉTIQUE DE L'ATOPIE CUTANÉE

(57) Abstract : A composition for topical application comprising : - at least one sucrose stearate comprising at least 70% by weight of monooesters of sucrose and of stearic acid, the rest being composed of diesters, triesters and polyesters of sucrose and of stearic acid, - and/or a sorbitan ester, for use in the therapeutic treatment of cutaneous atopy, as an agent for inhibiting the adhesion of Staphylococcus aureus to human nasal mucosa and skin.

(57) Abrégé : Composition pour application topique comprenant : - au moins un sucrose stéarate comprenant au moins 70% en poids de monooesters de sucrose et d'acide stéarine, le complément étant composé de di, tri, polyesters de sucrose et d'acide stéarine, - et/ou un ester de sorbitan pour utilisation dans le traitement thérapeutique de l'atopie cutanée comme agent inhibant l'adhésion de Staphylococcus aureus sur la peau et la muqueuse nasale humaine.
INHIBITION OF THE ADHESION OF PATHOGENIC MICROORGANISMS BY A SUCROSE STEARATE AND/OR A SORBITAN ESTER IN THE COSMETIC TREATMENT OF CUTANEOUS ATOPY

SUMMARY OF THE INVENTION

The invention relates to a cosmetic treatment process for human atopic dermatitis based on coating the surface of the skin with a cosmetic composition that forms a film on it. According to the invention, this film—by virtue of its constituents—inhibits the adhesion of pathogenic micro-organisms to the skin and reinforces the skin barrier.

More specifically, the cosmetic composition contains an ester of sucrose and/or an ester of sorbitan capable of blocking the adhesion of Staphylococcus aureus to the skin and nasal mucosa, thereby inhibiting the proliferation of pathogenic flora. The effect of this inhibition is to protect the cutaneous barrier by limiting the breakdown of lipids, especially ceramides, which is indirectly due to Staphylococcus aureus.

PRIOR ART

Atopic dermatitis or cutaneous atopy is an inflammatory, pruriginous skin condition associated with a hereditary immune predisposition and abnormalities of the cutaneous barrier. In clinical terms, this hereditary predisposition can also manifest as allergic rhinitis and asthma.

Atopic dermatitis leads to hypersensitivity to environmental allergens which are tolerated by healthy subjects.

In atopic dermatitis, eczema represents a delayed-type hypersensitivity reaction mediated by Th2 lymphocytes (which produce IL-4 and IL-5) and antigen-presenting cells.
Like any immune reaction mediated by antigen-specific T lymphocytes, the inflammatory reaction of the eczema of atopic dermatitis proceeds through three phases.

The first phase is asymptomatic sensitisation. This phase is clinically inapparent and leads to the amplification of antigen-specific T lymphocytes. Typically, sensitisation occurs in young childhood through exposure to environmental allergens which are captured by dendritic cells.

In a second phase, eczema develops. After re-exposure to the allergen in question, Langerhans cells migrate and activate antigen-specific, cytokine-producing Th2 lymphocytes which, in turn, activate a variety of different cell-types in the skin. This mechanism helps recruit leukocytes into the dermis and epidermis where they produce inflammatory mediators. This phase of variable duration is characterised by eczema lesions. In most patients, it is accompanied by high levels of antigen-specific IgE antibodies, some of which are bound to the surface of Langerhans cells.

Finally, the lesions regress in the third phase. The eczema of atopic dermatitis develops in flare-ups separated by periods of spontaneous remission. The mechanisms involved in regulating the inflammation remain poorly understood.

Atopic dermatitis affects 10-30% of the population but its prevalence is constantly on the rise in developed countries, having doubled or tripled in the last twenty years.

Atopic dermatitis is characterised by pruriginous flare-ups of acute eczema separated by periods of remission. It is most common in children. It onsets a matter of months after birth in the form of lesions on the cheeks and areas of skin subject to rubbing. It then develops in the form of attacks between one and two years of age. During this time, the skin is dry and has red, oozing patches, especially on the inner surfaces of skinfolds. After five years of age, attacks tend to disappear but the skin remains dry and sensitive. In some people, atopic dermatitis can persist into adulthood.
Two phenomena follow on from atopic dermatitis. Firstly, the cutaneous barrier is weakened and secondly, the skin gets colonised by a flora of pathogenic micro-organisms.

The main tissue of the cutaneous barrier is the *stratum corneum*, the outermost layer of the epidermis comprised of corneocytes and special lipids, including cholesterol, free fatty acids, cerebrosides and ceramides. These lipids act as intercellular cement and make the *stratum corneum* water-proof.

Analysis of the *stratum corneum* of patients with atopic dermatitis show marked deficiencies in certain proteins and cutaneous lipids. There are deficiencies in both filaggrin, a protein involved in aggregating keratin filaments in corneocytes, and involucrin, a protein essential to constructing the protein skeleton of the *stratum corneum*. The lipids that are most notably deficient are ceramides 1 and 3.

Ceramides are particularly important in regulating skin barrier function by limiting the evaporation of water.

These protein and lipid deficiencies mean that corneocytes adhere to one another less strongly, compromising the cohesion and integrity of the *stratum corneum*. This manifests as a significant reduction in the thickness of the *stratum corneum* in these patients.

Atopic dermatitis manifests as a significant loss of cutaneous proteins and lipids which, as mentioned above, leads to evaporation of moisture and dry skin. This is known to make it easier for allergens to enter the skin.

Atopic dermatitis therefore triggers a vicious cycle: the evaporation of intracellular water leads to cutaneous dehydration and dry skin which in turn increases cutaneous permeability. Greater cutaneous permeability makes it easier for allergens to penetrate through the tissue which sustains the skin's irritability.
The skin's barrier function is also consolidated by the local ecosystem which consists of a flora of saprophytic bacteria.

A saprophytic bacterial flora is a natural, permanent feature of the surface of the skin. The density of bacteria on the surface of the skin is estimated at between $10^3$ and $10^5$/cm$^2$. The most common species are staphylococci, notably coagulase-negative *Staphylococcus epidermidis* and related species (*Micrococcus*) and coryneform bacteria, both aerobic (*Corynebacterium, Brevibacterium*) and anaerobic (*Propionibacterium acnes*). These bacteria are established on the *stratum corneum* where they adhere to corneocytes to form a protective biofilm.

This saprophytic bacterial flora therefore reinforces barrier function since it occupies potential adhesion sites for other micro-organisms—which might be pathogenic—and inhibit their proliferation.

However, if the skin is damaged as it is in atopic dermatitis, impaired cutaneous barrier function promotes water evaporation and creates a skin surface environment that is conducive to colonisation by bacteria, viruses or fungi. This permissive environment is exacerbated by the rise in skin temperature that occurs during an attack of eczema.

Thus, a pathogenic bacterial flora can grow temporarily on the surface of the skin. Most of these species are found in the normal environment, including species belonging to the genera *Pseudomonas* and *Acinetobacter*; others derive from the digestive or buccal flora such as enterobacteria, streptococci or species of the genus *Clostridium*.

These bacteria are not usually capable of proliferating on the surface of human skin but they can cause infection if cutaneous barrier function is compromised as in atopic dermatitis in which they can form a pathogenic bacterial biofilm.

Among the bacteria of the transient pathogenic flora, *Staphylococcus aureus* (*S. aureus*) is the potentially most pathogenic species being the most common member of the genus
which is found in the nasal passages and throat of 15-30% of healthy people. This Gram-positive bacterium establishes itself on the skin by adhering to skin cells.

Recent studies have shown that the skin of 90% of patients with atopic dermatitis is colonised by *S. aureus*, compared with with only 5% of healthy subjects. Remarkably, atopic dermatitis is also a proven risk factor for colonisation of the nasal mucosa by *S. aureus* which then provides a reservoir in the environment of atopic patients (Pascolini *et al*., 2011).

Some studies have also suggested that ceramides produced by the cutaneous flora are activated in the presence of *S. aureus*. Ceramidases hydrolyse ceramides in the *stratum corneum* which might suggest that colonisation of the skin by *S. aureus* is partly responsible for the deficiency in this type of lipid in the atopic epidermis (Kita *et al*., 2002).

*S. aureus* is also a source of superantigens (proteinaceous toxins) which, in subjects with atopic dermatitis, interact with immune cells, amplifying the inflammatory response and thereby triggering flare-ups.

There is therefore a tangible link between the proliferation of *S. aureus* on the epidermal surface and impairment of cutaneous barrier function as a result of ceramide deficiency, especially in atopic subjects (remembering that impaired barrier function promotes sensitisation to environmental allergens and maintenance of inflammation of the skin). The two main viruses responsible for infections are herpes simplex virus (HSV) and vaccinia virus. Colonisation by the yeast *Malassezia* has also been observed in patients with atopic dermatitis.

Current treatment modalities for atopic dermatitis are based on managing the inflammation and controlling bacterial colonisation.
Modalities aimed at managing the inflammation include the administration of glucocorticosteroids and calcineurin inhibitors like pimecrolimus and tacrolimus. These products are usually combined with emollient products.

Bacterial control has been extensively reported on, notably involving the administration of broad-spectrum antibiotics and the application of antiseptic solutions. First-line treatment is becoming difficult because of antibiotic-resistant bacteria. Moreover, both types of treatment not only kill the pathogens present on the skin but also the beneficial saprophytic bacteria.

The main disadvantage of both these modalities is that they destroy a component that is required for effective barrier function, namely the saprophytic bacterial flora.

Recent studies have shown that the topical application of compositions containing certain sugars inhibit the adhesion of pathogenic bacteria to the skin.

Document WO 2006/106220 reports that certain sugars—mono- and oligo-saccharides such as rhamnose, galactose, mannose and lauryl glucoside—inhibit the adhesion of bacteria to corneocytes from atopic dogs, especially bacteria of the genus *Staphylococcus* (*S. intermedius*).

Document WO 96/23479 suggests that certain sugars can be used to inhibit the adhesion of certain micro-organisms. Singled out are monosaccharides like raffinose, mannose and rhamnose, disaccharides, oligosaccharides, aminated sugars and esters of various sugars including esters of glucose such as cetearylglucoside, caprylglucoside and decyglucoside. These various sugars can be blended into the compositions of cosmetic or dermatological preparations to inhibit bacterial adhesion, e.g. that of *S. aureus*, and/or for therapeutic purposes, notably the treatment of atopic dermatitis.

Document EP0875239A2 lists various esters of sugars including esters of sucrose, for their activity against certain Gram-positive species like *Staphylococcus epidermidis*,
Staphylococcus aureus, Corynebacterium and Propionibacterium, involved in a list of pathologies on which atopic dermatitis appears. The esters listed are palmitate/stearate diester, stearate diester, laurate monoester, myristate monoester, and stearate triester and tetraester.

Document EP1340486A1 lists various sugar esters, including esters of sucrose, fructose, glucose and trehalose. Only the esters of fructose, glucose and trehalose are tested for their ability to inhibit the growth of Staphylococcus aureus. Sucrose esters are not tested for this activity. Only one representative of this family, namely sucrose stearate, is tested and this only for bleaching activity (see Table 7). Finally, this document does not address atopic dermatitis.

Document EP0815841A1 reports a composition to control skin redness due to nappies rubbing. This is not a treatment for atopic dermatitis as described above. This document describes the inhibitory effect on the growth of Staphylococcus aureus and Staphylococcus epidermidis of a mixture of monoesters of sucrose with palmitic acid and stearic acid or a mixture of monoesters with palmitic acid and lauric acid.

Document EP2210588A1 describes foaming compositions containing polysorbate 80, i.e. an ester of sorbitan. Polysorbate 80 is a very common emulsifying agent.

Mintel document (XP002693208) describes a moisturising composition containing sucrose stearate.

Document WO4/037225A2 describes compositions free of either alcohol or propylene glycol as a vehicle for foaming aerosols. Atopic dermatitis is mentioned among other diseases that could be treated using the aerosol supplemented with some specific active substance. Sucrose stearate and polysorbate 80 mentioned in the examples are commonly used a surface-active agents.
Document FR2798591A1 describes the use of special vegetable oil to enhance the synthesis of cutaneous lipids, in particular for the treatment of atopic dermatitis. Sucrose distearate and sorbitan tristearate are commonly used as surface-active agents.

MERCK document (XP-002693209) describes an anti-wrinkle composition containing sucrose stearate.

Document EP1639989A1 describes the generation of micro-emulsions containing esters of sugar or sorbitan used as surface-active agents.

In Examples 5 and 8 of document US2005/158348A1, the compositions respectively contain polysorbate 80 and a sucrose ester. These compositions are intended for the treatment of pain and inflammation. Esters of sorbitan and sucrose are used in the excipient.

Document US2010/080768A1 describes the presence of various ceramides and sphingolipids in compositions intended for the treatment of various diseases, including atopic dermatitis.

Document US2011/101135 describes using sorbitan monocaprylate as a preservative in a cosmetic composition. Various bacterial strains are tested, including Staphylococcus aureus.

There is nevertheless a need for more effective alternatives to the various modalities currently available for managing atopic dermatitis.

It is in this context that the Applicant discovered, surprisingly and unexpectedly, that certain sugar esters like esters of sucrose and sorbitan, strongly inhibit the adhesion of pathogenic micro-organisms to the skin and mucous membranes.
Inhibition of the adhesion of *S. aureus* to the surface of the skin prevents the proliferation of pathogenic micro-organisms, even in the absence of antibiotic or topical antiseptic.

One of the advantages of inhibiting the adhesion of pathogenic micro-organisms to the skin, in particular *S. aureus*, is to maintain the saprophytic bacterial flora and reinforce cutaneous barrier function by cutting down breakdown of its component lipids.

Sugar esters can be advantageously combined with lipids that occur naturally in the epidermis to form a film that acts still more effectively against breakdown of the epidermal barrier and colonisation of the skin by pathogens.

Other aims and aspects of the invention will emerge on reading the following detailed description which is given for the purposes of illustration and is in no way limiting.

**DETAILED DESCRIPTION OF THE INVENTION**

A first aspect of the invention relates to a cosmetic composition for topical application containing at least one sucrose ester and/or sorbitan ester as an agent to inhibit the adhesion of *Staphylococcus aureus* to human skin and nasal mucosa.

More specifically, the invention concerns a composition for topical application containing at least one sucrose ester and/or sorbitan ester for use in the treatment of atopic dermatitis, as an agent to inhibit the adhesion of *Staphylococcus aureus* to human skin and nasal mucosa.

A sugar ester is a sugar in which at least one free alcohol group has been esterified with a fatty acid chain.

A series of different families of sugar ester have been described. Notably, there are esters of glucose, sucrose and sorbitan (Piccicuto *et al.*, 2001). They have the advantage of being
non-toxic and non-irritant and are therefore in widespread use in the food processing, pharmaceutical and cosmetic industries, often for their surface-active properties.

Out of these three distinct families, this Application only concerns esters of sucrose and sorbitan.

These are non-ionic surfactants with a hydrophilic group consisting of sucrose or sorbitan joined through an ester linkage to a hydrophobic group consisting of a fatty acid. The surface-active properties of these esters also make them easily to combine with lipids in cosmetic compositions, especially emulsions.

α-D-glucopyranosyl-β-D-fructofuranoside or sucrose carries eight free alcohol groups and can therefore be esterified with up to eight fatty acids.
Sorbitan is generated by the dehydration of sorbitol, a polyhydroxylated compound which is itself obtained by reducing the aldehyde group of glucose to create an alcohol group.
Sorbitan carries four free alcohol groups, each of which can be esterified by a fatty acid.

In the context if the present invention, sorbitan esters means esters of the "Span" type, e.g. with the following developed structural formula:

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\[ \text{in which } R \text{ is a fatty acid, in this case a monoesterified span} \]
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The present invention also concerns "Tween"-type polyethoxylated sorbitan esters, e.g. the following formula:
in which R is a fatty acid, in this case a monoesterified tween.

The carbon chains of the fatty acids may be short or long, e.g. mention could be made of lauric acid, myristic acid, palmitic acid and stearic acid with respective chains of C_{12}, C_{14}, C_{16} and C_{18}. The fatty acid may also be chosen from among saturated and unsaturated fatty acids, e.g. oleic acid (a C_{18} carbon chain).

Thus, according to another characteristic of the invention, the cosmetic composition contains sucrose and/or sorbitan with at least one alcohol group esterified with a fatty acid from the group with carbon chains of between C_{12} and C_{22}, advantageously between C_{12} and C_{18}.

Depending on the ratio of fatty acids to sucrose, esterification can yield the monoester, diester, triester or polyester (up to the octa-ester), or a mixture of all these forms. The esterification of sorbitan can yield the monoester, diester, triester, tetra-ester or a mixture of these various forms.

According to another embodiment, the cosmetic composition of the invention contains sucrose and/or sorbitan in which some or all of the alcohol groups have been esterified with the same fatty acid.

In this case and advantageously, the sucrose ester will be selected from the group containing sucoolaurate, sucromyristate, sucropalmitate and sucrostearate, and the sorbitan ester will be selected from the group containing sorbitan laurate (Span 20), sorbitan monostearate (Span 60), sorbitan oleate (Span 80) and sesquioleate sorbitan (Montane 83).
In an advantageous embodiment, the sucrose ester is a sucrose stearate containing at least 70%, advantageously at least 75% monoesters of sucrose and stearic acid by weight, the rest being di, tri and polyesters of sucrose and stearic acid.

Advantageously, the cosmetic composition according to the invention contains a polyethoxylated sorbitan ester. Mention could be made of the ethoxylated sorbitan monolaurate (Polysorbate 20), polyoxyethylene sorbitan monostearate 20 (Polysorbate 60) and polyoxyethylene sorbitan mono-oleate (Polysorbate 80). In a preferred embodiment, the sorbitan ester is polysorbate 20 or polysorbate 80.

According to an alternative embodiment, the cosmetic composition can be made up with sucrose and/or sorbitan in which some or all of the alcohol groups have been esterified with at least two different fatty acids.

In this case and advantageously, the sucrose ester will be selected from the group containing sucralpalmitate stearate and sucrotetrastearate triacetate, and the sorbitan ester will be selected from the group containing the oleate/stearic acid ester of sorbitan (Montane 481) and sorbitan esterified with fatty acids from olive oil (olivate sorbitans).

According to a preferred embodiment, the sucrose ester in the cosmetic composition according to the invention is the sucrostearate, i.e. sucrose esterified with at least one molecule of stearic acid (a C₁₈ fatty acid).

Those skilled in the art are aware that, for a given fatty acid carbon chain length, the proportion of monoesters in the mix will affect the hydrophobicity/hydrophilicity of the sugar ester.

These properties are characterised by means of the Hydrophile/Lipophile Balance (HLB) index. A value of between 1 and 10 indicates a lipophilic sugar ester, corresponding to relatively few monoesters and therefore a relatively high proportion of polyesters. But a
value of between 11 and 20 indicates a hydrophilic sugar ester, corresponding to a high proportion of monoesters and therefore a relatively low proportion of polyesters.

In a particular embodiment of the invention, the sucrostearate has a HLB of 16, corresponding to a relative proportion of sucrose monoesters and stearic acid of between 75% and 80% in weight. Hereafter, this product is referred to as sucrose monostearate.

Preferably, the sucrose ester and/or the sorbitan ester represents 0.1-5% of the composition by weight, advantageously between 1% and 3%.

Advantageously, the cosmetic composition also contains lipids that are capable of restoring the cutaneous barrier, respectively:

- at least one lipid not found naturally in the skin, advantageously an oil; and/or
- a mixture of constituents that occur naturally in the skin, including ceramides 1, 3, 6, cholesterol, free fatty acids and phytosphingosine.

In practice, supplementation with certain specific lipids can help restore the lipid layer between skin cells, i.e. the extracellular cement, thereby helping to restore the cutaneous barrier. As a result, the evaporation of water from the skin is cut down together with the risk of *S. aureus* adhering on the surface of the skin and proliferating there. This action combines with the effects of the esters of the invention which inhibit the adhesion of *S. aureus* and prevent the hydrolysis of ceramides in the *stratum corneum*.

Lipids that are not naturally found in the skin, like oils, mediate short-term moisturisation of the tissue. They are advantageously selected from the group including sunflower oil and rapeseed oil (canola) because of the high concentrations of essential omega-6 and omega-3 fatty acids in these oils.

In a particular embodiment of the invention, the cosmetic composition contains lipids not found naturally in skin, respectively sunflower oil representing 3-15% of the composition by weight and rapeseed oil (canola) representing 0.05-10% of the composition by weight.
Supplementation with lipids that occur naturally in the skin can correct the deficiency in certain *stratum corneum* lipids seen in patients suffering from atopic dermatitis. This can help restore a functional cutaneous barrier in the long term, especially when combined with the effects of the esters described above.

In a particular embodiment, the mixture of naturally-occurring constituents corresponds to a lipid composition with an INCI designation, namely Water, Ceramide 3, Ceramide 6II, Ceramide 1, Phytosphingosine, Cholesterol, Sodium Lauroyl Lactylate, Carbomer, Xanthan Gum. This lipid composition is advantageously supplied as a commercial product, SK Influx V™ (Evonik Industries).

Preferably, the lipid composition represents 0.01-5% of the overall composition by weight.

Advantageously, the cosmetic composition also contains at least one additional polyhydroxylated compound selected from the group containing rhamnose, xylitol and mannitol.

These additional polyhydroxylated compounds like rhamnose and xylitol help inhibit the adhesion of pathogenic bacteria such as *S. aureus* to human skin and nasal mucosa. Mannitol also has free radical-quenching activity.

In a particular embodiment of the invention, the cosmetic composition contains a mixture of three of the additional polyhydroxylated compounds mentioned above.

Advantageously, rhamnose represents 0.01-1% of the composition by weight, xylitol represents 0.05-2% of the composition by weight and mannitol represents 0.005-1% of the composition by weight.

Advantageously, the composition also contains at least one anti-pruriginous agent selected from the group containing in particular:

- palmitoyl ethanolamide, CAS Number 544-31-0;
- hydroxy-α-sanshoool, CAS Number 83883-10-7, part of the composition of zanthalène™;
- a lipo-dipeptide based on tyrosyl-arginine, part of the composition of calmosensine™;
- ichtyol or ammonium ichthosulphonate, CAS Number 8029-68-3.

Advantageously, the cosmetic composition according to the invention can also include at least one anti-inflammatory agent, preferably selected from the group containing:
- beta-sitosterol, CAS Number 83-46-5;
- enoxolone or glycyrrhetinic acid, CAS Number 471-53-4.

Advantageously, the cosmetic composition also includes Vitamin PP which is known to stimulate lipid synthesis in the stratum corneum, including that of ceramides, free fatty acids and cholesterol. Vitamin PP acts by stimulating the activity of serine palmitoyl transferase, a key enzyme in the synthesis of sphingosine which is the precursor for ceramide production.

Another aspect of the invention concerns a cosmetic composition for the cosmetic treatment of atopic dermatitis.

The invention also concerns a cosmetic treatment process for atopic dermatitis based on forming a film on the skin to protect the epidermis by means of the composition described hereafter.

In an advantageous embodiment, the treatment process involves applying to the skin a film-forming composition, notably containing a sucrose and/or sorbitan ester to inhibit the adhesion of *S. aureus* to the surface of the skin, together with lipids, e.g. fatty acids, ceramides and cholesterol, to reinforce the skin's defences against insults from micro-organisms, and notably against enzymes secreted by such micro-organisms that hydrolyse constituents of the stratum corneum.
This film can be applied to the skin according to the stage of the disease, in order to:
- arrest its progress;
- act during flare-ups of the disease;
- prevent recurrence.

Advantageously, the composition used to stop progression contains (in percentage weight of the composition):
- between 1% and 5% sucrose monostearate and/or a sorbitan ester;
- between 3% and 25% of a mixture of oils;
- between 0.01% and 5% SK Influx V\textsuperscript{TM};
- between 0.06% and 4% of a mixture of rhamnose, xylitol and mannitol.

Advantageously, the composition used to treat flare-ups contains (in percentage weight of the composition):
- between 1% and 5% sucrose monostearate and/or a sorbitan ester;
- between 3% and 25% of a mixture of oils;
- between 0.01% and 5% SK Influx V\textsuperscript{TM};
- between 0.06% and 4% of a mixture of rhamnose, xylitol and mannitol;
- between 0.01% and 1% of an anti-pruriginous agent;
- between 0.5% and 1% of an anti-inflammatory agent;

Advantageously, the composition used notably to prevent recurrence contains (in percentage weight of the composition):
- between 1% and 5% sucrose monostearate and/or a sorbitan ester;
- between 3% and 25% of a mixture of oils;
- between 0.01% and 5% SK Influx V\textsuperscript{TM};
- between 0.06% and 3% of a mixture of rhamnose, xylitol and mannitol;
- between 0.01% and 1% of an anti-pruriginous agent;
- between 0.01% and 2% Vitamin PP.
These various compositions are film-forming, i.e. they can create a film over the surface of the skin to protect it against insults from pathogenic micro-organisms.

A number of advantages emerge from reading about the invention:

- reducing *S. aureus* adhesion to atopic skin prevents the growth of a pathogenic bacterial flora at the same time as maintaining the saprophytic bacterial flora;

- it is known that a bacterial biofilm grows on the surface of the skin in a series of different phases from bacterial adhesion through growth, maturation and expansion of the film. Therefore, inhibiting the adhesion of *S. aureus* to atopic skin leads to inhibition of the formation of a pathogenic biofilm;

- using a non-toxic, non-irritant sucrose and/or sorbitan ester cuts down the need for antimicrobial agents such as antibiotics and topical antiseptic products;

- the presence of lipids that do not occur naturally in the skin restores barrier function and helps cut down the evaporation of water from the epidermis;

- complementary action by the sucrose and/or sorbitan ester and the lipids reduces the burden of *S. aureus* as a result of the inhibition of adhesion and then restores the stratum corneum's barrier function;

- the sucrose and/or sorbitan ester and the lipids therefore form a film on the epidermis that protects it against insults from pathogenic micro-organisms and prevents breakdown of the barrier function.
EXAMPLES

1/ EFFECT OF SUCROSTEARATE ON IN VITRO ADHESION OF STAPHYLOCOCCUS AUREUS ONTO A SOLID MATRIX.

1) Method

The following protocol was used:

- *S. aureus* was grown in the Clinical Bacteriology Laboratory at La Timone Hospital (CIP 65-8) in 'Nutrient Broth N° 2' (Oxoid), for 12 hours at 37°C;

- The culture was centrifuged at 9,000 g for 10 min and then the bacterial pellet was resuspended in phosphate-buffered saline (PBS);

- This suspension was diluted 50-fold in an aqueous solution or in an aqueous solution containing the test polyhydroxylated compound. This was either xylitol or sucrostearate HLB 16 (SURFHOCETM C1816);

- The bacteria were pre-incubated with the test polyhydroxylated compound for 45 min at 37°C;

- The mixture (100 µl) was then spotted into a well on a glass cytology slide, of fixed surface area (0.8 cm²) with walls, i.e. a special slide for cell culture (Chamber Slide System, Labtek);

- The bacterial cultures were then incubated at 37°C for 60 min after which they were rinsed with UltraPure water to wash off any bacteria that had not stuck to the surface of the well;

- Adherent bacteria were stained with Crystal Violet for 10 seconds, rinsed and dried at 25°C for 12 hours;

- Finally, the bacteria were examined by microscope at a magnification of X 1,000 (oil immersion) with perfectly homogeneous fields;

- Finally, the number of bacteria in each well was counted automatically using appropriate software.
2) Results

In this protocol, the effect of the polyhydroxylated compounds was analysed vis-a-vis inhibition of the adhesion of *S. aureus* onto the solid matrix. The tests were carried out with xylitol at a final concentration of 0.5% and the HLB16 sucrostearate (sucrose monostearate, SURFHOPE C18-C16) at a final concentration of 1%.

Table 1: Effects of xylitol (0.5%) and HLB 16 sucrostearate (1%) on the adhesion of *S. aureus* to the surface of glass slides. Results are presented as the mean count of three fields together with the corresponding standard deviation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cells per field</th>
<th>Inhibition of adhesion (% with respect to the water control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (control)</td>
<td>99 ± 11</td>
<td>0%</td>
</tr>
<tr>
<td>Xylitol (0.5%)</td>
<td>91 ± 6</td>
<td>8%</td>
</tr>
<tr>
<td>HLB 16 sucrostearate (1%)</td>
<td>12 ± 1</td>
<td>88%</td>
</tr>
</tbody>
</table>

3) Conclusion

Strong inhibition of the adhesion of *S. aureus* to the surface of glass slides was observed in the presence of 1% HLB 16 sucrostearate.

2/ Effect of Esters of the Invention on Ex Vivo Adhesion of *S. aureus* on Human Corneocytes.

To corroborate the *in vitro* findings, an *ex vivo* adhesion test on human corneocytes was adapted from a method developed on dogs (McEwan et al., 2005).
1) Bacterial strain

A clinical strain of *S. aureus* (CIP 65-8) was isolated from a patient in the Clinical Bacteriology Laboratory at La Timone Hospital in Marseille.

2) Protocol

*S. aureus* was inoculated into 10 ml of ‘Nutrient Broth N° 2’ (Oxoid) and incubated with stirring at 37°C for 12 hours. The culture was centrifuged and the bacterial pellet was resuspended in PBS. Bacterial density was adjusted to about $10^6$ CFU/ml with osmotically purified water.

Target areas were marked out on the arms of a human volunteer. On each area, cutaneous debris was removed with 5 successive "pre-stripping" procedures with discs of Sellotape™Original (diameter 22 mm). Corneocytes were then collected from each target area using D-Squame™ sticky discs (diameter 22 mm) with a D-Squame disc applicator set to a pressure of 150 g/cm².

The discs were then placed in Petri dishes (diameter 35 mm) and covered with 0.5 ml water or 0.5 ml of a suspension of *S. aureus* at a density of $10^6$ CFU/ml, containing the test polyhydroxylated compound (triplicate areas for each).

The polyhydroxylated compounds tested in this way were:
- xylitol, at a final concentration of 0.5%;
- HLB 16 sucrose stearate (sucrose monostearate, SURFHOPE C1816, ) at a final concentration of 1%,
- sucrose laurate monoester (SURFHOPE C1216, 80% monoester), at a final concentration of 0.1%,
- polysorbate 60, at a final concentration of 0.1%;
- polysorbate 60, at a final concentration of 1%;
- polysorbate 20, at a final concentration of 0.1%;
All solutions were made up in water and put in contact with *S. aureus* at room temperature 45 min before the start of the adhesion experiment. The dishes were then incubated at 37°C for 60 min. Then the discs were rinsed in osmotically purified water to remove any bacteria that had not stuck to the corneocytes. Adherent bacteria were stained with oxalated Crystal Violet for 10 seconds. Finally, the discs were rinsed off with osmotically purified water, placed on a microscope slide and air-dried for 24 hours.

3) Image acquisition and bacterial counts

Adherent bacteria were photographed using an Olympus BX 53 microscope fitted with a digital camera. The images were then analysed using UTHSCSA Image Tool software (Reindeer Graphics Inc.). The mean number of bacteria per disc was calculated from 10-12 images, corresponding to the surfaces of about 100 corneocytes. Means were compared using Statgraphics Plus software (Manugistics Inc.).

4) Results and conclusion

These test results show that xylitol inhibits the adhesion of *S. aureus* to corneocytes by a factor of about 20% (Table 2). Very strong inhibitory activity—50% or over—was observed with the HLB 16 sucrose ester and polysorbate 60 at final concentrations of 1% (Table 2). Polysorbate 20 and 60 at 0.1% gave very promising inhibitory activity. In contrast, sucrose laurate monoester induced a significant increase in adhesion.
Table 2: Effect of xylitol and sugars of the invention on the adhesion of *S. aureus* on human corneocytes.

<table>
<thead>
<tr>
<th>Polyhydroxylated compound (final concentration)</th>
<th>Inhibition of <em>S. aureus</em> adhesion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylitol (0.5%)</td>
<td>Test 1: 21.0</td>
</tr>
<tr>
<td>HLB 16 sucrostearte (1%)</td>
<td>Test 1: 57.0</td>
</tr>
<tr>
<td>Sucrose laurate (0.1%)</td>
<td>Test 1: -22.8</td>
</tr>
<tr>
<td>Polysorbate 60 (0.1%)</td>
<td>Test 1: 39.8</td>
</tr>
<tr>
<td>Polysorbate 60 (1%)</td>
<td>Test 1: 54.0</td>
</tr>
<tr>
<td>Polysorbate 20 (0.1%)</td>
<td>Test 1: 57.0</td>
</tr>
</tbody>
</table>

Each sugar was tested in two independent experiments for xylitol and sucrose stearate (1%).

These *ex vivo* results therefore confirm the *in vitro* results, i.e. that the presence of HLB 16 sucrostearte in its surroundings inhibits the adhesion of *S. aureus* to both a solid matrix like a cytology slide and to human corneocytes.

**3/ EXAMPLES OF TOPICAL COMPOSITIONS**

**ATODERM™ STOP EVOLUTIVE**

<table>
<thead>
<tr>
<th>Product</th>
<th>% by weight in the composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLB 16 sucrostearte (SURFHOPE C1816)</td>
<td>2.0.</td>
</tr>
<tr>
<td>Lipid phase</td>
<td>11.0.</td>
</tr>
<tr>
<td>Other polyhydroxylated compounds</td>
<td>0.61.</td>
</tr>
<tr>
<td>Water</td>
<td>Q.s. 100</td>
</tr>
</tbody>
</table>
### ATODERM™ STOP CRISE

<table>
<thead>
<tr>
<th>Product</th>
<th>% by weight in the composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLB 16 sucrostearate (SURFHOPE C1816)</td>
<td>2.0.</td>
</tr>
<tr>
<td>Lipid phase</td>
<td>11.0.</td>
</tr>
<tr>
<td>Other polyhydroxylated compounds</td>
<td>0.61.</td>
</tr>
<tr>
<td>Anti-pruriginous agent</td>
<td>0.3.</td>
</tr>
<tr>
<td>Anti-inflammatory agent</td>
<td>0.5.</td>
</tr>
<tr>
<td>Water</td>
<td>Q.s. 100</td>
</tr>
</tbody>
</table>

### ATODERM™ STOP RECIDIVE

<table>
<thead>
<tr>
<th>Product</th>
<th>% by weight in the composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLB 16 sucrostearate (SURFHOPE C1816)</td>
<td>2.0.</td>
</tr>
<tr>
<td>Lipid phase</td>
<td>11.0.</td>
</tr>
<tr>
<td>Other polyhydroxylated compounds</td>
<td>1.1.</td>
</tr>
<tr>
<td>Anti-pruriginous agent</td>
<td>0.3.</td>
</tr>
<tr>
<td>Vitamin PP</td>
<td>0.3.</td>
</tr>
<tr>
<td>Water</td>
<td>Q.s. 100</td>
</tr>
</tbody>
</table>
REFERENCES


CLAIMS

1/ Composition for topical application, comprising:
   - a sucrose stearate containing at least 70% monoesters of sucrose and stearic acid
     by weight, the rest being di, tri and polyesters of sucrose and stearic acid,
   - and/or a sorbitan ester
   for use in the treatment of atopic dermatitis as an agent to inhibit the adhesion of
   Staphylococcus aureus on human skin and nasal mucosa.

2/ Composition according to Claim 1, wherein the sucrose stearate contains at least 75%
   monoesters of sucrose and stearic acid by weight, the rest being di, tri and polyesters of
   sucrose and stearic acid, with a HLB of 16 (sucrose monostearate).

3/ Cosmetic composition according to Claim 1, wherein at least one of the sorbitan's
   alcohol groups is esterified with a fatty acid selected from the group of fatty acids with
   a carbon chain of between C_{12} and C_{22}.

4/ Cosmetic composition according Claim 3, wherein the at least one of the sorbitan's
   alcohol groups is esterified with a fatty acid selected from the group of fatty acids with
   a carbon chain of between C_{12} and C_{18}.

5/ Cosmetic composition according to any of one of Claims 1 to 4, wherein all or some of
   the sorbitan's alcohol groups are esterified with the same fatty acid.

6/ Cosmetic composition according to any of one of Claims 1 to 5, wherein all or some of
   the sorbitan's alcohol groups are esterified with at least two different fatty acids.

7/ Cosmetic composition according to any of one of Claims 1 to 6, wherein the sorbitan
   ester is polyethoxylated.
8/ Composition according to Claim 1, wherein the sorbitan ester is polysorbate 20 or polysorbate 60.

9/ Cosmetic composition according to any one of Claims 1 to 8, wherein the sucrose stearate and/or the sorbitan ester represent 0.1-5% of the composition by weight.

10/ Cosmetic composition according to any one of Claims 1 to 7, wherein the sucrose stearate and/or the sorbitan ester represent 1-3% of the composition by weight.

11/ Cosmetic composition according to any of one of Claims 1 to 19, wherein the composition further comprises lipids that can restore cutaneous barrier function, respectively:
   - at least one lipid not found naturally in the skin, advantageously an oil; and/or
   - a mixture of constituents that occur naturally in the skin, including ceramides 1, 3, 6, cholesterol, free fatty acids and phytosphingosine.

12/ Cosmetic composition according to Claim 11, wherein the mixture of constituents that occur naturally in the skin corresponds to a lipid composition with an INCI designation, namely: Water, Ceramide 3, Ceramide 6II, Ceramide 1, Phytosphingosine, Cholesterol, Sodium Lauroyl Lactylate, Carbomer, Xanthan Gum, representing between 0.01% and 5% of the composition by weight.