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(54) Titre : COMPOSITIONS DERMATOLOGIQUES COMPRENANT DES INHIBITEURS DE PROLIFERATION
MICROBIENNE

(54) Title: DERMATOLOGICAL COMPOSITIONS COMPRISING MICROBIAL PROLIFERATION INHIBITORS

(57) **Abrégé/Abstract:**

Dermatological and/or cosmetic compositions allowing the appearance of the symptoms of hypersensitivity and cutaneous intolerance to be avoided, comprise an effective combination of microbial proliferation inhibitors containing (a) a first microbial proliferation inhibitor which comprises an aqueous mixture of sodium polyacrylate, at least one polyol and at least one glycol compound of formula (I): $R_1-O-O(R_2-O)_nR_3$ in which R_1 and R_3 are independently H or a straight or branched C1-C5 alkyl group; R_2 is a straight or branched C1-C5 alkylene group and n is between 1 and 400,000, and (b) a second microbial proliferation inhibitor which comprises at least one monoalkyl glycerine ether or an ester thereof of formula (II): $R_4OCH_2CH(OH)CH_2OR_5$ which R_4 is a straight or branched chain alkyl group containing 6 to 24 carbon atoms and R_5 is H or a straight or branched alkanoyl group containing 8 to 24 carbon atoms. The invention relates to the local or topical application of this composition as well as its use as a medicament, in particular for the treatment of the symptoms of hypersensitivity and cutaneous intolerance, psoriasis, atopy, acne and cutaneous ageing or for the prevention of the symptoms of benign estival light eruption.



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(54) Title: DERMATOLOGICAL COMPOSITIONS (57) Abstract Dermatological and/or cosmetic compositions allowing the appearance of the symptoms of hypersensitivity and cutaneous intolerance to be avoided, comprise an effective combination of microbial proliferation inhibitors containing (a) a first microbial proliferation inhibitor which comprises an aqueous mixture of sodium polyacrylate, at least one polyol and at least one glycol compound of formula (I): $R_1-O-O(R_2-O)_nR_3$ in which R_1 and R_3 are independently H or a straight or branched C1-C5 alkyl group; R_2 is a straight or branched C1-C5 alkylene group and n is between 1 and 400,000, and (b) a second microbial proliferation inhibitor which comprises at least one monoalkyl glycerine ether or an ester thereof of formula (II): $R_4OCH_2CH(OH)CH_2OR_5$ which R_4 is a straight or branched chain alkyl group containing 6 to 24 carbon atoms and R_5 is H or a straight or branched alkanoyl group containing 8 to 24 carbon atoms. The invention relates to the local or topical application of this composition as well as its use as a medicament, in particular for the treatment of the symptoms of hypersensitivity and cutaneous intolerance, psoriasis, atopy, acne and cutaneous ageing or for the prevention of the symptoms of benign estival light eruption.		

DERMATOLOGICAL COMPOSITIONS COMPRISING MICROBIAL PROLIFERATION INHIBITORS

FIELD OF THE INVENTION

- 5 The present invention relates to a dermatological composition containing no chemical preservative, no perfume and no colouring agent and allowing the appearance of the symptoms of hypersensitivity and/or cutaneous intolerance to be avoided at the time of its topical application.

10 BACKGROUND OF THE INVENTION

Sensitive or reactive skins are skins which easily react to allergens or irritants following disorders of cutaneous permeability linked to the alteration of the barrier function of the stratum corneum and to an imbalance in the production of epidermic cytokines.

15

The modification of the cutaneous permeability gives rise to the appearance of subjective and objective signs.

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The appearance of subjective signs is particularly observed when ordinary cosmetic or hygiene products are used. They are defined by itching, twinging, pricking, glowing, stinging and burning sensations.

25

The objective signs are shown in an irregular fashion by xerosis, by seborrheic dermatitis, by telangiectasia, by squames, by flushing, by vesicles or even by an edema.

30

According to specialists the subjective and objective signs can appear for a short time immediately after application of the cosmetic product or can be indicated in a transitory fashion or can persist for a longer period of time; all day or in an intermittent fashion during the day. Thus, these signs can be discreet or severe and can require a medical opinion.

Persons who show the symptoms of hypersensitivity and cutaneous intolerance can be:

- carriers of dermatosis (atopy, seborrheic dermatitis)
- subjects who have been subjected to traumatisms (sunburn, burns)
- 5 - subjects with no previous dermatological history but in whom the subjective and objective signs are present
- subjects who have previously had medicinal treatments.

Thus, it has recently been shown that, except for cosmetic or hygiene products used daily, several factors linked to age, sex, lifestyle and the profession of
10 patients as well as the environment, appear to intervene in cutaneous sensitisation or irritation.

Among these factors, the age of the patient is a significant factor. In fact, infants show a more significant cutaneous sensitivity than adults. Women have more significant hypersensitivity problems and cutaneous intolerance
15 than men. Hormonal cyclic variations greatly influence the reactivity of a woman's skin. In the same way emotions, the stress of daily life, the consumption of alcohol and spicy food, the use of water and detergents during the day, variations in temperature, pollution, also appear to influence the appearance of cutaneous sensitivity.

20 However, specialists still question the short-term and long-term consequences of the phenomena of hypersensitivity and cutaneous intolerance. Recent studies have shown that no link exists between intolerant skin and the presence of a pre-existing illness. On the contrary, certain studies lead one to believe that the fact of having a sensitive or reactive skin is a factor which
25 encourages a contact allergy. In addition, the in-vivo evaluation of the phenomena of cutaneous irritations by measuring the imperceptible loss of water from the epidermis, has shown that a cutaneous irritation can lead to an

interruption of the hydrolipidic film of the surface thus causing an increase in the epidermic loss of water and therefore cutaneous ageing.

It is known from the prior art that certain components of cosmetic or hygiene products, such as chemical preservatives, perfumes, colouring agents,
5 chemical sun screens and ethanol, can cause problems of irritation and/or cutaneous intolerance, even contact allergy problems.

Therefore, the Applicant has sought a solution to the problems of hypersensitivity and cutaneous intolerance by producing a dermatological or cosmetic composition containing no active or raw ingredient of preservative
10 type which could be a potential irritant or allergenic agent.

Dermatological or cosmetic products for non-sterile topical application are exposed to the risks of microbiological contamination during the manufacture, during their packaging and above all during their use by the patient or consumer.

15 For this reason, it is common in the prior art:

- to introduce chemical preservatives, such as parabens and formol donors,
 - to introduce natural preservatives, such as essential oil extracts,
 - to formulate with a minimum quantity of water,
 - 20 - to change certain physical factors in the formulation, such as pH, activity of water (a_w) and redox potential,
 - to incorporate cationic surfactants which have anti-microbial properties,
 - to use biological systems such as certain proteins and/or enzymes,
 - to use ethanol
- 25 in order to better preserve the products.

However, the chemical and/or natural preservatives and the cationic surfactants, despite their anti-microbial power, often cause intolerance reactions, such as irritations and/or allergies.

Moreover, the development of cosmetic products either under conditions of extreme pH or by reducing the quantity of water in the formulation and/or the activity of the water (a_w) by an increased quantity of sugar and salt in order to prevent microbial proliferation, no longer satisfies the requirements of scientists and consumers.

The use of certain thickening agents has been proposed such as polyacrylates and polymethacrylates and their derivatives (cf. Patents FR 2 682 296 and WO 97/05856) as anti-microbial compounds in cosmetic compositions. The latter interfere with the activity of water (a_w) and exercise a strong osmotic effect on the environment, which allows the inactivation of micro-organisms introduced in a cosmetic or pharmaceutical preparation by depriving them of water.

However, their use remains limited, mainly because of the relatively high concentrations which are necessary to obtain the desired anti-microbial effect. At these concentrations, the composition obtained cannot be handled in an efficient manner by the consumer as it is difficult to spread and its consistency is too sticky. In addition, its poor aesthetic appearance does not encourage the consumer to use it again.

The use of hygroscopic agents has also been proposed such as polyols of glycerine, propylene glycol or PEG type as anti-microbial agents. However, their use also remains limited as the high concentrations of this type of compound required to obtain an effective anti-microbial action encourage the active ingredients of the composition to penetrate too deep. The latter then enter into the systemic circulation of the individual and can cause undesirable side effects while seeing their initial topical properties poorly exploited or reduced.

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The use of monoalkyl glyceryl ethers in antimicrobial compositions is known.
(See EP-A-0747047, FR-A-27229050, DE-A-4140474 and US-A-5621012)

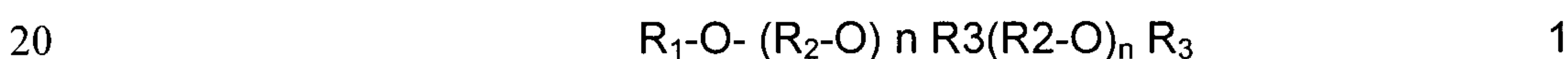
AMENDED SHEET

SUMMARY OF THE INVENTION

A principal subject of the present invention is a dermatological or cosmetic composition containing no chemical preservative, no perfume and colouring agent and allowing the appearance of the symptoms of hypersensitivity and/or cutaneous intolerance to be avoided. The composition is characterized in that it contains a synergistic mixture of two inhibitors of microbial proliferation.

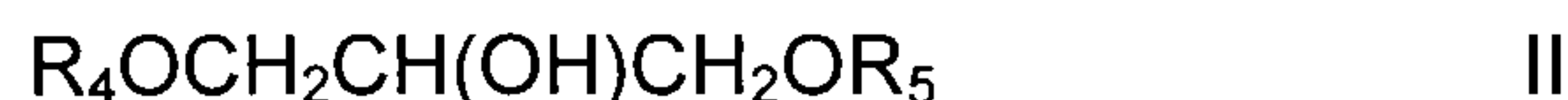
The inventors have discovered that the simultaneous presence of these two inhibitors of microbial proliferation allows, thanks to a synergistic effect, the mechanism of which is not yet completely elucidated, the substantial reduction in their concentrations. These reduced concentrations allow the desired microbial effect to be obtained without the disadvantages observed during the individual use of these inhibitors.

The present invention therefore provides a dermatological and/or cosmetic composition allowing the appearance of the symptoms of hypersensitivity and cutaneous intolerance to be avoided, said composition being characterized in that it contains an effective combination of microbial proliferation inhibitors containing (a) a first microbial proliferation inhibitor which comprises an aqueous mixture of sodium polyacrylate, at least one polyol and at least one glycol compound of formula 1



in which R_1 and R_3 are independently H or a straight or branched C1-C5 alkyl group; R_2 is a straight or branched C1-C5 alkylene group and n is between 1 and 400,000,

and (b) a second microbial proliferation inhibitor which comprises at least one monoalkyl glycerine ether or an ester thereof of formula II



in which R_4 is a straight or branched chain alkyl group containing 6 to 24 carbon atoms and R_5 is H or a straight or branched alkanoyl group containing 8 to 24 carbon atoms.

The invention also relates to a dermatological and cosmetic composition which may contain, in addition, at least one polysaccharide gum, such as modified cellulose and/or at least one polysaccharide gum obtained by fermentation such as xanthan gum and/or sclerotium gum, preferably a mixture of these two
5 last-named products.

The cosmetic or dermatological compositions for topical application are often formulated in the form of emulsions. An emulsion is formed by the dispersion of two non-miscible liquids using a surfactant. The emulsions are thermodynamically unstable systems and the stability of an emulsion can be
10 improved by increasing the viscosity of the dispersed and dispersing phases. Moreover, it is known from the prior art that certain gelling agents can stabilise an emulsion without using a surfactant (cf. Patent WO 96/37180).

Another subject of the present invention is the use of immunomodulating molecules, preferably a synthetic peptide to modulate the secretion of
15 inflammation mediators and cytokines as the result of cutaneous irritations.

Allergens are substances which are recognised as "foreign" by the defence system of the skin and induce a contact hypersensitivity or allergy. They are part of our environment. They are present in the air such as pollens, animal hairs, in the water such as calcium salts, in numerous common cosmetic and
20 hygiene products such as perfumes, chemical preservatives, colouring agents and chemical sun screens.

During an allergic or hypersensitivity reaction certain elements of the immune system react violently against the allergens. Therefore, the introduction of an allergen into the skin triggers an acute reaction which manifests itself by an
25 edema, by flushing and by symptoms which manifest themselves later in a prolonged fashion. The inflammation is expressed by an increase in vascular

permeability, an orientated afflux of immunocompetent cells (such as lymphocytes, monocytes, macrophages) and the production of inflammation modulators (such as histamine) of cytokines (such as lymphokines, monokines interleukins and interferons) and neurohormones (such as
5 propiomelanocortine, melanotropin, adrenocorticotrope).

All the epidermic cells: keratinocytes, Langerhans' cells, melanocytes and Merkel's cells can secrete inflammation mediators, cytokines and certain neurohormones when faced with a cutaneous irritation. Under normal conditions, the production of cytokines by the epidermic cells is low, however, it
10 is increased during any attack on the epidermis. This hypersecretion and colonisation of tissues by immunocompetent cells are harmful to the organism and need to be modulated as they can damage the tissues.

Therefore, the invention also relates to a dermatological and cosmetic composition as described above and which contains, in addition, an
15 immunoregulating molecule, preferably a synthetic peptide.

Another subject of the present invention is the use of this dermatological and cosmetic composition as described above for the treatment of the symptoms of psoriasis.

Another subject of the present invention is the use of this dermatological and
20 cosmetic composition as described above for the treatment of the symptoms of atopy.

Another subject of the present invention is the use of this dermatological and cosmetic composition as described above for the treatment of the symptoms of acne.

Another subject of the present invention is the use of this dermatological and cosmetic composition as described above for the treatment of the symptoms of cutaneous ageing.

Another subject of the present invention is the use of this dermatological and cosmetic composition as described above for the preparation of sun creams and in particular for the prevention of benign estival light eruption.

This invention as described above is more particularly intended for cosmetic or dermatological use. More particularly, this dermatological or cosmetic composition according to the invention is applied by topical route.

The invention also relates to the use of this dermatological composition described above as a medicament as well as the use of its constituents for the preparation of a medicament intended for the treatment of the symptoms described above.

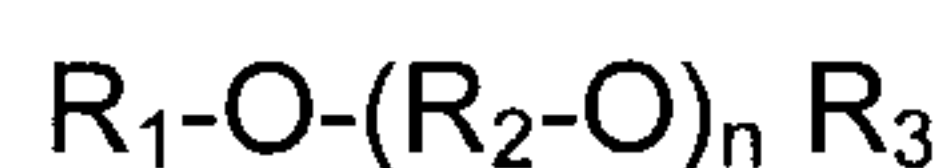
BRIEF DESCRIPTION OF THE FIGURE

The present invention will now be described in a more detailed fashion and with reference to Figure 1 which represents the influence of the composition according to the invention on the reduction of itching sensations after 24 days of treatment.

DETAILED DESCRIPTION OF THE INVENTION

First microbial proliferation inhibitor containing sodium polyacrylate

The first microbial proliferation inhibitor is an aqueous mixture of sodium polyacrylate, at least one polyol and at least one glycol compound of formula 1



in which R_1 and R_3 are independently H or a straight or branched C1-C5 alkyl group; R_2 is a straight or branched C1-C5 alkylene group and n is between 1 and 400,000.

The polyol may be a diol or triol containing 3 to 8 carbon atoms (for example
 5 propylene glycol, 1,3-butylene glycol, 1,2-pentanediol, 1,2-octanediol (INCI name caprylyl glycol), 1,8-octanediol, 2-ethyl-1,3-hexanediol, glycerine (1,2,3-propanetriol), mannitol, sorbitol or mixtures thereof). Preferably the polyol is a mixture of glycerine and caprylyl glycol.

The glycol compound of formula 1 may be a monoether of diethyleneglycol or
 10 triethyleneglycol or may be a polyalkyleneglycol. Preferred glycol compounds of formula 1 include methoxydiglycol, ethoxydiglycol, propoxydiglycol, butoxydiglycol and triethyleneglycol monopropyl ether. Preferred esters of glycol compounds of formula 1 include ethoxyethanol acetate and ethoxydiglycol acetate. Preferred polyalkyleneglycols include
 15 polyethyleneglycols (for example PEG-8) and polypropyleneglycols.

The amounts of the components of the first microbial proliferation inhibitor present as percentages by weight of the first microbial inhibitors are

	sodium polyacrylate	0.2 to 1% (preferably 0.5 to 0.8% most preferably 0.6 to 0.7%)
20	polyol	40 to 70% (preferably around 50 to 60%)
	glycol compound of formula 1	0 to 35% (preferably 10 to 30, most preferably 15 to 25%)

Examples of suitable first microbial proliferation inhibitors are sodium
 25 polyacrylate / glycerin / ethoxydiglycol / caprylyl glycol / aqua and sodium polyacrylate / glycerine / PEG-8 / caprylyl glycol / aqua sold by the Sederma company under the denominations Osmocide®, Osmocide 2® and Osmocide 3®.

The concentrations of these commercially available materials containing sodium polyacrylate can generally vary from 5 to 25% by weight, the preferred concentrations are usually situated between 10 to 20% by weight relative to the total weight of the composition.

5

Second microbial proliferation inhibitor comprising an alkyl glycerine ethers and/or alkyl esters thereof

Suitable alkyl glycerine ethers are monoalkyl ethers of glycerine and alkyl
10 esters thereof of formula II



in which R_4 is a straight or branched chain alkyl group containing 6 to 24 carbon atoms and R_5 is H or a straight or branched alkanoyl group containing 8 to 24 carbon atoms. There can be mentioned amongst others: octoxyglycerine
15 (Sensiva SC50®, Phagogene) octoxyglyceryl behenate, octoxyglyceryl palmitate, batyl alcohol (Nikkol Batyl Alcohol 100®, Nikko, Nikkol Batyl Alcohol EX®, Nikko), batyl isostearate (Nikkol GM-181S®, Nikko) and batyl stearate (Nikkol GM-18S®, Nikko).

The concentration of the alkylglycerine ether and/or an alkyl ester thereof
20 generally varies between 0.1 and 2% by weight relative to the weight of the total composition, the preferred concentrations being situated between 0.25 and 1.25% by weight.

Optionally, polysaccharide gums can be used as gelling agents in the the compositions according to the present invention. Suitable polysaccharide
25 gums include:

- the derivatives of modified cellulose, carboxymethyl cellulose (Blanose 7H 3SF®, Aqualon), carboxymethyl hydroxyethyl

- cellulose (Aqualon), hydroxypropyl cellulose (Klucel H[®], Klucel M[®], Klucel E[®], Aqualon), hydroxyethyl cellulose (Natrosol 250 H[®], Natrosol 250 HR[®], Natrosol 250 MR[®], Aqualon), cetyl hydroxyethyl cellulose (Natrosol 330 CS[®], Aqualon),
- 5 hydroxypropyl methyl cellulose (Methocel E[®], Methocel F[®], Methocel J[®], Methocel K[®], Dow Chemical).
- the derivatives of carrageenans, copolymer of sulphoesters of galactose and 3-6-anhydrogalactose (Genugel RLV[®], Aqualon),
 - the derivatives of alginates, glyceryl alginate (Karajel[®], Chimilux),
 - 10 sodium alginate (Manucol[®], SPCI),
 - The derivatives of guar, guar gum (Jaguar C[®], Rhône-Poulenc), hydroxypropyl guar (Jaguar HP-8[®], Jaguar HP-60[®], Jaguar HP-79[®], Jaguar HP-120[®] and Jaguar HP-200[®], Rhône-Poulenc) and hydroxypropyl guar hydroxypropyltrimonium chloride (Jaguar
 - 15 C-162[®], Rhône-Poulenc),
- and/or polysaccharide gums obtained by the fermentation of bacteria such as:
- xanthan gums originating from the fermentation of carbohydrates by *Xanthomonas campestris* (Rhône-Poulenc)
 - sclerotium gums originating from the fermentation of
 - 20 carbohydrates by *Sclerotium rolfsii* (Amigel[®], Alban Muller)
 - gellan gums originating from the fermentation of carbohydrates by *Pseudomonas elodea* (Kelcogel[®], Kelco).

The concentration of gelling agents, preferably xanthan gum, sclerotium gum and cetyl hydroxyethylcellulose generally varies between 0.05 and 5% by weight relative to the total weight of the composition, the preferred

25 concentrations are situated between 0.1 and 2.5% by weight.

Immunomodulating molecules

Several immunomodulating molecules can be used to form the compositions according to the invention. The selection between these molecules can be easily carried out by a person skilled in the art. There can be mentioned
5 amongst others synthetic peptides, biotechnological macromolecules, glycyrrhetic acid and its stearic ester (Grhethinol-O® and SGS®, Maruzen), plant extracts and extracts from fish eggs such as salmon teleosts (Gamma Nucleotides Marins®, Seporga).

In a preferred fashion, it is desirable to use immunomodulators which have a
10 minimal number of amino acids situated around 3 or more, preferably around 3 to 8, and which confer on the molecule its immunomodulating properties. This type of peptide chain is coupled with an alkyl chain, usually lipidic, the function of which is to stabilise the molecule and to prevent rapid enzymatic degradation of the peptide chain. In particular, it is desirable to use
15 immunomodulators which do not have antimicrobial properties. In particular, the use of lipoamino acids or antibacterial lipids as described in the Patent FR 2 734 158 is undesirable within the context of the present invention.

Among the preferred synthetic peptides with the context of the present invention, there can be mentioned:

- 20 - the alkyl peptides (such as Modulene®, Seporga, in which the peptide sequence is biomimetic of the human melanotropin terminal fraction). The linear or branched alkyl chain contains between 5 and 22, in particular between 8 and 17 carbon atoms.
- 25 - melanin activating peptide (MAP®, Seporga), the peptide sequence is derived from human melanotropin.
- epidermal thymosin factor (ETF®, Seporga), the peptide sequence is derived from thymuline.

- cytokin inhibiting factor (Melipren®, Seporga).

Among the biotechnological macromolecules preferred within the context of the present invention, there can be mentioned:

- 5 - glycoproteins of yeasts (Immucell®, Pentapharm)
- glycoproteins of the walls of *Enterobacteriae hafnia*
- glycoproteins of the walls of *Klebsiella pneumoniae*
- betaglucan and its copolymers (Polyglucadyne®, Brooks)
- polysaccharides of yeasts such as glucopyranose (Irialin®, Iris,
- 10 Drieline®, Alban Muller and Glucanne®, Sederma)
- microbiological ferment of *Corynebacterium granulosum*
(Langherine®, Sederma).

Among the plant extracts preferred within the context of the present invention, there can be mentioned:

- 15 - tropical plant extracts such as Cola, Maté and Guarana (Quench
 T®, Pentapharm)
- extract of the leaves of *Perilla frutescens* (Shiso®, Jan Dekker)
- extract of Harpagophyton (Flachmann)
- extract of Coralline (Coralline®, Codif/ADF)
- 20 - extract of the root of Echinacea (Echinacea®, Indena).

The concentration of active immunomodulator generally varies between 0.5 and 10% by weight relative to the total weight of the composition, the preferred concentrations being situated between 1 and 5% by weight.

The dermatological and/or cosmetic compositions of the present invention may
25 in addition contain the standard cosmetic and pharmaceutical (dermatological)
excipients used such as mineral and vegetable oils, silicon fluids, fatty acids

and alcohols, waxes, hydrating agents, vitamins, sequestering agents or any other ingredient usually used in beauty care and dermatology.

The above-mentioned compositions according to the invention can be incorporated into an oil-in-water emulsion, or a water-in-oil emulsion, a
5 water-in-silicone fluid emulsion or a water-in-oil-in-water multiple emulsion. Emulsions contain an oil phase an aqueous phase and an emulsifier to form and stabilise the emulsion. Alternatively the compositions of the present invention may be incorporated into a gel or a pseudo-emulsion (dispersion of two non-miscible phases using gelling agents).

10 The oil phase of emulsions according to the present invention can contain for example:

- 1) hydrocarbon oils such as paraffin or mineral oils such as isohexadecane and isododecane;
- 2) natural oils such as sunflower oil, onager oil, jojoba oil, hydrogenated
15 castor oil, avocado oil, hydrogenated palm oil;
- 3) natural triglycerides such as caprylic/capric triglyceride, caprylic/capric linoleic triglyceride, caprylic/capric succinic triglyceride;
- 4) silicon fluids such as cyclomethicone, dimethicone and dimethiconol;
- 5) fatty alcohols such as stearic alcohol, cetyl alcohol, hexadecylic alcohol;
- 20 6) fatty acids such as stearic acid, palmitic acid;
- 7) esters of fatty acids such as dioctyl succinate, glyceryl dioleate, myristyl myristate and isopropyl myristate;
- 8) waxes such as beeswax, paraffin, carnauba wax, ozokerite;
- 9) lanolin and its derivatives (oil, alcohol, waxes);
- 25 10) their mixtures.

The oil phase preferably comprises approximately 5 to 30% and preferably 10 to 20% by weight of the composition.

The emulsifiers which can be used in the emulsions according to the present invention can be selected from the emulsifiers known in the prior art as being suitable for use in the types of emulsions listed above. Suitable emulsifiers include:-

- 5 1) The sucroesters such as saccharose cocoate and saccharose distearate;
- 2) The esters of sorbitan and the esters of ethoxylated sorbitan such as sorbitan stearate or polysorbate;
- 3) The esters of glycerols, the esters of ethoxylated glycerols and
10 polyglycerols such as glyceryl oleate or PEG-20 glyceryl stearate or polyglyceryl-10-stearate;
- 4) The ethoxylated fatty alcohols such as ceteth-12 or steareth-6;
- 5) The sesquioleates such as sorbitan sesquioleate;
- 6) The emulsifiers based on silicon fluid such as silicon polyols;
- 15 7) The ethoxylated sterols of soya; or a mixture of one or more of the emulsifiers mentioned above.

The quantity of emulsifiers optionally present in the oil-in-water or the water-in-oil compositions of the present invention is, preferably, from 0.5 to 15% by weight of the composition. The quantity of emulsifiers present in the
20 water-in-oil-in-water multiple emulsion is, preferably approximately 7 to 20% by weight of the composition.

The oil phase of pseudoemulsions according to the present invention may comprise any of the materials listed above as the oil phase of emulsions.

The gels or pseudo-emulsions can be prepared by using one or a combination
25 of several gelling agents selected from the gelling agents acceptable in cosmetic or dermatological products. These gelling agents can also, if desired be incorporated into the emulsions of the present invention. Examples of suitable gelling agents include:-

- 1) polysaccharide gums such as the derivatives of modified celluloses, derivatives of carraghenans, derivatives of alginates and derivatives of guar;
- 2) polysaccharide gums obtained from the fermentation of bacteria such as Xanthan gum, Sclerotium gum and Gellan gum;
- 3) acrylic polymers such as carbomers, polyacrylates, polymetacrylates and their derivatives;
- 4) quaternized polymers;
- 5) PVP's and polymers derived from PVP; and
- 6) mixtures thereof.

In the preferred pseudo-emulsion or in gelled emulsions according to the present invention, the gelling agent or combination of gelling agents represents approximately 0.1 to 30% and preferably approximately 0.25 to 25% by weight of the composition.

In addition, the compositions according to the present invention may contain one or more other compounds which will be known by persons skilled in the art, for example:

- 1) electrolytes for the stabilization of the water-in-oil emulsion such as sodium chloride or magnesium sulphate, preferably in a quantity ranging from 0.2 to 4% by weight of the composition;
- 2) moistening agents such as glycerine or propylene glycol or PEG or sorbitol, preferably in a quantity ranging from 1 to 10% by weight of the composition;
- 3) sequestering agents such as tetrasodium EDTA, preferably in a quantity ranging from 0.01 to 0.5% by weight of the composition;
- 4) softeners such as the ethers of fatty acids or the esters of fatty acids, preferably in a quantity ranging from 0.5 to 10% by weight of the composition;

- 5) hydrating agents such as hyaluronic acid, NaPCA, preferably in a quantity ranging from approximately 0.01 to 5% by weight of the composition;
- 6) film forming agents to facilitate spreading over the surface of the skin, such as the hydrollysates of the proteins of oats, wheat, collagen and almond, preferably in a quantity ranging from approximately 0.1 to 5% by weight of the composition;
- 7) insoluble pigments such as titanium oxide, rutile titanium oxide, octahedrite titanium oxide, pyrogenic titanium oxide, micronized titanium oxide, titanium oxide surface treated with silicons or with amino acids, or with lecithins, or with metallic stearates, iron oxide, iron oxide surface treated with silicons or with amino acids, or with lecithin, or with metallic stearates, zinc oxide, micronized zinc oxide, mica covered with titanium oxide, preferably in a quantity ranging from approximately 0.5 to 5% by weight of the composition;
- 8) mixtures thereof

In all that follows and in all that has gone before, the percentages are given by weight except where indicated to the contrary.

Other characteristics and advantages of the invention will become apparent in the examples which follow and are given purely by way of illustration and are in no way limitative. In the Examples that follow the first microbial proliferation inhibitor is an aqueous mixture of sodium polyacrylate (about 0.65%), glycerine (about 52%), caprylyl glycol (about 6%) and ethoxydiglycol (about 20%) sold under the trade name Osmocide by Sederma. The alkyl peptide/dextran component is an alkyl peptide supplied by Seporga under the trade name Modulene

Example 1: Day cream (oil-in-water pseudo-emulsion)**Table 1: Composition of oil phase**

INCI Name	Concentration (% weight)
Beeswax	2 %
Isohexadecane	4 %
Diethyl Succinate	2 %
Isododecane	3.5 %
Glyceryl Dioleate	3 %
Cetyl Alcohol	2 %
Stearic acid	1 %

Table 2 : Composition of water phase

INCI Name	Concentration (% weight)
Sclerotium Gum	0.35 %
Xanthan Gum	0.35 %
Cetyl Hydroxyethylcellulose	0.35 %
Glycerin	5 %
Octoxyglycerin	1 %
Nylon-12	2 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3%
Aqua	to 100%

The gelling agents (sclerotium gum, xanthan gum and cetyl
5 hydroxyethylcellulose) are heated to 40°C in 30 ml of water under slow
mechanical agitation in order to obtain a translucent gel. Moreover, the other

half of the aqueous phase containing the glycerine as well as the oil phase are heated to 80°C.

The aqueous phases and the oil phase were then mixed at 80°C under vigorous agitation. The temperature is maintained at 80°C for 15 minutes and
5 the emulsion is cooled down to 60°C. The first microbial proliferation inhibitor is introduced into the emulsion at this temperature. The other ingredients: octoxyglycerin, alkyl peptide and nylon-12 are added at 30°C. The emulsification is continued until the cream is completely homogeneous.

Comparative Example 2 : Day cream (oil-in-water pseudo-emulsion)

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Table 3 Composition of oil phase

INCI Name	Concentration (% weight)
Beeswax	2 %
Isohexadecane	4 %
Dioctyl Succinate	2 %
Isododecane	3.5 %
Glyceryl Dioleate	3 %
Cetyl Alcohol	2 %
Stearic acid	1 %

Table 4 : Composition of aqueous phase

INCI Name	Concentration (% weight)
Sclerotium Gum	0.35 %
Xanthan Gum	0.35 %
Cetyl Hydroxyethylcellulose	0.35 %
Glycerin	5 %
Octoxyglycerin	1 %
Nylon-12	2 %
Alkyl Peptide/Dextran	3 %
Aqua	to 100 %

The same production process is used as in the preparation of Example 1.

Example 3 : Day cream (oil-in-water emulsion containing a liquid crystal phase)

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Table 5 : Composition of oil phase

INCI Name	Concentration (% weight)
Cyclomethicone	5 %
Diocetyl succinate	3 %
Polyacrylamide/C13-14	3 %
Isoparaffin/Laureth-7	
Palmitic acid	1 %
C12-16 Alcohols	1 %

Table 6 : Composition of aqueous phase

INCI Name	Concentration (% weight)
Sclerotium Gum	0.3 %
Hydrogenated lecithin	2 %
Glycerin	5 %
Octoxyglycerin	1 %
Nylon-12	2 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3%
Aqua	to 100 %

The hydrogenated lecithin, 2 % glycerine and 30 ml of water are heated to 70°C under slow mechanical agitation for 30 minutes until hydration of the lecithin is complete. Moreover, the other half of the aqueous phase containing
5 the glycerine at 3 % is used to form the Sclerotium gum gel. In order to do this, the gum and the glycerine are heated at 70°C under slow mechanical agitation.

Before emulsification, the aqueous phases are mixed at 70°C under slow agitation until a homogeneous phase is obtained. The emulsification is carried out by introducing the oil phase, which is also heated to 70°C, into the aqueous
10 phase under vigorous agitation. The emulsion is cooled down under moderate agitation. The same production process as in Example 1 is used to introduce the first microbial proliferation inhibitor, octoxyglycerin, alkyl peptide and nylon-12.

Example 4 : Body milk (oil-in-water emulsion)**Table 7 : Composition of oil phase**

INCI Name	Concentration (% weight)
Isohexadecane	8 %
Mineral oil	5 %
Phenyl dimethicone	0.5 %
Cetyl alcohol	0.5 %
Ceteth-20	2 %
Sorbitan stearate	2 %

Table 8 : Composition of aqueous phase

INCI Name	Concentration (% weight)
Sodium carbomer	0.35 %
Glycerin	5 %
Octoxyglycerin	1 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3%
Aqua	to 100 %

The same production process is used as in the preparation of Example 1.

Example 5 : Body cream (water-in-oil emulsion)**Table 9 : Composition of oil phase**

INCI Name	Concentration (% weight)
Isohexadecane	6 %
PEG-30 Dipolyhydroxystearate	1 %
Cyclomethicone/PPG-15 Stearyl Ether	3 %

Table 10 : Composition of aqueous phase

INCI Name	Concentration (% weight)
Magnesium sulphate	0.8 %
Glycerin	5 %
Octoxyglycerin	1 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3%
Aqua	to 100 %

The same production process is used as in the preparation of Example 1.

Example 6 : Eye contour soothing gel**Table 11: Composition of aqueous gel**

INCI name	Concentration (% weight)
Carbomer 980	0.50 %
Xanthan Gum	0.20 %
PEG-8	4 %
Octoxyglycerin	1 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3 %
Hafnia extract	0.03 %
Sodium Hyluronate	0.12 %
Methylsilanol Aspartate Hydroxyprolinate	5 %
Tocopheryl Acetate	0.05 %
Tetrasodium EDTA	0.05 %
Sodium hydroxide	0.15 %
Aqua	to 100 %

The gelling agents (Carbomer 980 and xanthan gum) are heated at 60°C in 30
 5 ml of water under slow mechanical agitation in order to obtain a transparent gel
 (Phase A).

Moreover, the sodium hyaluronate is dissolved at 40°C in 20 ml of water under
 magnetic stirring (Phase B).

The remainder of the aqueous phase is used to dissolve (at ambient
 10 temperature) the PEG-8, tetrasodium EDTA, tocopheryl acetate, methylsilanol
 aspartate hydroxyprolinate, Hafnia extract, alkyl peptide and octoxyglycerin
 (Phase C).

In order to obtain the final product, Phase A, Phase B and the first microbial
 proliferation inhibitor are mixed together under moderate mechanical agitation.

When the temperature of the gel reaches ambient temperature, Phase C is added. The pH is adjusted with sodium hydroxide.

Example 7 : Day cream (water-in-oil-in water emulsion)

Table 12 : Composition of primary emulsion

INCI Name	Concentration (% weight)
Oil phase	
Glyceryl Isostearate	2 %
PEG-7 Hydrogenated castor oil	0.2 %
Mineral oil/Quaternium 18 hectorite/Propylene Carbonate	0.2 %
Caprylic/Capric Triglyceride	6.4 %
Cyclomethicone	1.6 %
Internal aqueous phase	
Glycerin	0.8 %
Magnesium Sulphate	0.28 %
Aqua	to 40 %

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Table 13 : Composition of the external aqueous phase

INCI Name	Concentration (% weight)
Carbomer 980	0.10 %
Acrylates/C10-30/ Alkyl Acrylate Crosspolymer	0.60 %
Octoxyglycerin	1 %
First microbial proliferation inhibitor	10 %
Alkyl peptide/Dextran	3 %
Tetrasodium EDTA	0.05 %
Sodium hydroxide	0.15 %
Aqua	to 60 %

The multiple emulsion is prepared according to a two-stage production process.

The first stage consists of producing an oily continuous phase primary emulsion. This is carried out by introducing the internal aqueous phase, heated to 80°C, into the oil phase which is also heated to 80°C under vigorous agitation. Agitation is maintained until ambient temperature is achieved.

The second stage comprises the incorporation of the external aqueous phase containing the gelling agents and the active ingredients into the primary emulsion under weak agitation at ambient temperature. Agitation is maintained until the formation of the multiple emulsion. For the preparation of the external aqueous phase the same production process as in Example 1 is used. At the end of emulsification the pH is adjusted using sodium hydroxide.

Example 8 : Sun cream (water-in-oil emulsion)

Table 14 : Composition of oil phase

INCI Name	Concentration (% weight)
Cyclomethicone/Dimethicone Copolyol	6 %
PEG-7 Hydrogenated Castor oil	2 %
Cyclomethicone	2 %
Isocetyl stearate	3 %
PEG-45 Dodecyl Glycol Copolymer	2 %
PPG-3 Myristyl Ether	2 %
Hydrogenated Polyisobutene/Titanium Dioxide	27 %
C12-15 Alcohols Benzoate	2 %
Tocepherol	0.05 %

Table 15 : Composition of the aqueous phase

INCI Name	Concentration (% weight)
Magnesium sulphate	0.25 %
Tetrasodium EDTA	0.05 %
Hafnia extract	0.02 %
PEG-8	4 %
Octoxyglycerin	1 %
First microbial proliferation inhibitor	15 %
Alkyl peptide/Dextran	3 %
Aqua	to 100 %

The same production process is used as in the preparation of Example 1.

Inhibition of microbial proliferation of the combination of the first and second microbial proliferation inhibitors.

The microbial proliferation inhibitory activity (bacteriostatic and/or fungistatic) of a basic material can be determined by measuring its minimal inhibitory concentration (MIC). This corresponds to the smallest quantity of basic material required to completely inhibit the growth of bacteria or of the yeast tested.

Method for determining the minimal inhibitory concentration (MIC) :

The bacteria of a pure strain of *Staphylococcus epidermidis* (Cocci Gram +) IP 8155T are removed and inoculated in a trypticase-soya liquid medium in order to revivify them for the preparation of mother solutions. The inoculum is produced in such a fashion as to obtain 10^6 bacteria/ml after incubation in an

aerobic atmosphere for 24 hours at 37C. The quantity of bacteria in the suspension is determined by spectrophotometry.

For the determination of the microbiostatic activity, the Mueller Hinton gelose nutrient medium is melted and distributed into Petri dishes.

- 5 The samples of basic material tested are prepared extemporaneously. Depending on the basic materials, a successive dilution range is prepared from the mother solution. The necessary quantities are removed from these dilutions and are poured onto the gelose.

- 10 Counting of the inoculum is also carried out by the method of decimal dilutions and the necessary quantities of are then deposited on the gelose containing the basic material tested. The Petri dishes are incubated at 37°C for 24 hours.

After incubation for 24 hours, the Petri dishes are examined to determine the concentration of basic material for which there is no culture visible to the naked eye. The lowest concentration at which there was no culture visible is the MIC.

Table 16 : Results of the MIC of the first and second microbial proliferation inhibitors

Basic material tested	Concentration %	Activity
First microbial proliferation inhibitor	5	+
	10	+
	15	+
	20	+
	25.40	+
	26.26	-
	30	-
	35	-
	40	-
Octoxyglycerine	0.1	+
	0.5	+
	1	-
Combination of first microbial proliferation inhibitor and octoxyglycerine	15 + 0.5	-

The MIC results show that the first microbial proliferation inhibitor has a power to inhibit microbial proliferation starting from 26.26% and the alkyl glycerine ether has an activity starting from 1%. The use of a combination of these two basic materials below their MIC demonstrates a synergistic action.

The dermatological and cosmetic products of the present invention are exposed to the risk of microbiological contamination during their production, their packaging and during their use. For this reason, the effectiveness of the microbial protection of the product must be ensured vis à vis external

contamination with the purpose of obtaining a permanent bacteriological quality.

The **challenge test** allows the resistance of a cosmetic product to microbial development to be estimated. This study which is also called "superinfection test", consists of introducing a determined number of known microorganisms, followed by examinations at given times in order to know whether they can survive and multiply. It is supposed to simulate a contamination which occurs during production, packaging or use of the product. This quantitative and qualitative study also allows the selection, in appropriate quantities, of the most effective and the most suitable preservatives for each cosmetic product tested.

Challenge test procedure

The strains of bacteria, yeasts and moulds used in this study are

- bacteria: *Staphylococcus epidermidis* (Cocci Gram +) IP 8155 T

Escherichia coli (Bacille Gram -) IP 52167

15 *Pseudomonas aeruginosa* (Bacille Gram -) IP 5842

Pseudomonas cepacia (Bacille Gram -) IP 8024 T

- yeast: *Saccharomyces cerevisiae* IP 118179 (ATC 2601)

- mould: *Aspergillus niger* IP 143183 (ATC 16404)

The mother solutions of micro-organisms are prepared as in the MIC method. Briefly, the colonies of bacteria, yeasts and moulds are removed and inoculated in the appropriate nutrient medium (trypticase-soya liquid medium for the bacteria and Sabouraud liquid medium for the yeasts and moulds) in order to revive them. The inoculums are carried out so as to obtain 10^6 micro-organisms/ml after incubation. Each inoculum tube is placed for 24 hours at 37°C for the bacteria and for 72 hours at 30°C for the yeasts and moulds.

The cosmetic products tested are introduced into sterile flasks and contaminated with mother solutions of the micro-organisms (T_0). For each micro-organism a different flask is contaminated and the flasks are stored at ambient temperature. At the end of 7 days (T'_0) a second contamination is
5 carried out by repeating the previous operation. The product thus polluted is stored at ambient temperature throughout the entire duration of the challenge test.

At the end of the challenge test each contaminated flask is homogenized and
10 for each flask a dilution of 1/10 is carried out in Eugon LT100 broth. The tubes are placed at 37°C for 24 hours and the quantity of living micro-organism is determined by bioluminescence.

The results of the challenge test confirm the MIC results. The same synergistic action is observed for all the micro-organisms tested when the first and second
15 microbial proliferation inhibitors are present in the compositions. By way of example, the results obtained with the bacteria *Staphylococcus epidermis* are shown in Tables 17 and 18. On the other hand, similar tests carried out with the composition of Example 2 have shown that this composition was immediately contaminated by the strains described previously.

Table 17 : Results of the challenge test on the composition according to the invention containing 15% of the first microbial proliferation

Time	Relative light unit
T ₁	24100
T ₂	6444
T ₇	65
T' ₁	25399
T' ₂	101
T' ₇	89

Table 18 : Results of the challenge test on the composition according to the invention containing 15% of the first microbial proliferation inhibitor and 1% of octoxyglycerine

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Time	Relative light unit
T ₁	13151
T ₂	4114
T ₇	60
T' ₁	255
T' ₂	86
T' ₇	95

Detection of the protective effect of the composition according to the invention for hypersensitive and intolerant skins : Stinging Test

Nowadays, it is necessary to ensure that products for topical application are well tolerated without provoking particular reactions such as stinging when they are applied to sensitive areas of the body. To this end, Frosch and Kligman in 1977 perfected a "Stinging Test" in order to determine the intensity of the reactivity of the skin.

The test consists of applying an aqueous solution of lactic acid at a concentration varying from 2 to 10% and physiological saline solution on the nasogenic folds. In fact, this region is known to be particularly reactive as it has a more permeable corneous layer. Moreover, it is rich in hair follicles and sweat glands which encourage the penetration of products applied to the skin and its sensory nerve network is particularly developed. In man, each hair follicle is associated with a specialized nerve ending which gives it a particular sensitivity to touch and pain.

Stinging is a form of pain which is well tolerated by patients. It develops rapidly after the appropriate stimulation of the sensory nerves. In the Stinging Test, evaluation of the stinging sensation is carried out during the first 30 seconds, at 2 minutes and at 5 minutes, by marking from 0 to 3. The score is established by calculating the difference in the sums of the total scores for each sulcus, between the side treated with lactic acid and that treated with physiological saline solution. This test is redone several times with modified protocols depending on the case.

In order to evaluate the protective effect of the present invention on patients who have sensitive and intolerant skins, the stinging test is used according to the following procedure. The study is carried out on 20 female subjects aged between 25 and 50. The subjects are selected from subjects presenting a

positive stinging test and having had no local treatment during the week preceding the study.

To qualify the positive stinging test subjects, a 10% aqueous solution of lactic acid is applied using a cotton bud on the left nasogenic sulci of each subject.

- 5 The right nasogenic sulci of the subjects are used for the application of a placebo, physiological saline solution. The stinging sensation at 10 seconds, 2.5 minutes and 5 minutes is evaluated. The quantification of the stinging sensation is determined on a numerical scale ranging from 0 to 3. The corresponding scores 0 to 3 signify:

10	0 = absence of stinging	1 = slight sensation
	2 = moderate sensation	3 = intense sensation

After this evaluation, an **overall score** for the stinging sensation is calculated for each time measurement.

- 15 **Overall score** = (Σ scores for lactic acid) - (Σ scores for physiological saline solution).

- 20 In order to evaluate the protective effect of the present invention, the product studied is applied on the left nasogenic sulcus and on the left cheek of each subject morning and night for 24 days and the physiological saline solution on the other side under the same conditions. On the 23rd day, the same procedure as that for the qualification of the subjects is repeated. The results obtained are shown in Figure 1.

The use of the composition according to the invention for 24 days allows a reduction in cutaneous activity of 43% to be detected in subjects having a hypereactive or intolerant skin.

CLAIMS

1. Dermatological or cosmetic composition comprising an effective combination of:
 - (a) a first microbial proliferation inhibitor which comprises a mixture of sodium polyacrylate, glycerine, caprylyl glycol, aqua, and ethoxydiglycol or PEG-8; and
 - (b) a second microbial proliferation inhibitor which comprises at least one monoalkyl glycerine ether or an ester thereof selected from octoxyglycerine, octoxyglyceryl behenate, octoxyglyceryl palmitate, batyl alcohol, batyl isostearate, and batyl stearate,wherein the composition contains no active or raw ingredient of preservative type and allows the appearance of symptoms of hypersensitivity and cutaneous intolerance to be avoided.
2. Composition according to claim 1, in which the monoalkyl glycerine ether is octoxyglycerine.
3. Composition according to either one of claims 1 and 2, further comprising at least one polysaccharide gum.
4. Composition according to claim 3, in which the polysaccharide gum is cetylhydroxyethylcellulose.
5. Composition according to claim 3, in which the polysaccharide gum is obtained by fermentation.
6. Composition according to claim 5, wherein the gum is sclerotium gum or xanthan gum.
7. Composition according to any one of claims 1 to 6, further comprising an immunomodulating molecule.

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8. Composition according to claim 7, in which the immunomodulating molecule is an alkyl peptide in which the peptide sequence is biomimetic of the human melanotropin terminal fraction and the alkyl moiety is a linear or branched alkyl chain containing between 5 and 22 carbon atoms.

9. Composition according to any one of claims 1 to 8, in which the combination of the microbial proliferation inhibitors is present in a quantity of approximately 0.25 to 30% by weight of the composition.

10. Composition according to claim 1, in which the mixture of sodium polyacrylate, glycerine, caprylyl glycol, aqua, and ethoxydiglycol or PEG-8 is present in a quantity of approximately 10 to 20% by weight of the total composition.

11. Composition according to claim 10, wherein the PEG-8 is present in a quantity of approximately 15% by weight of the total composition.

12. Composition according to claim 9, in which the monoalkyl glycerine ether or ester thereof is present in a quantity of approximately 0.25 to 1.25% by weight of the total composition.

13. Composition according to claim 12, in which the monoalkyl glycerine ether or ester thereof is present in a quantity of approximately 0.5% by weight of the total composition.

14. Composition according to any one of claims 3 to 6, in which the polysaccharide gum is present in a quantity of approximately 0.05 to 5% by weight of the total composition.

15. Composition according to claim 7 or 8, in which the immunomodulating molecule is present in a quantity of approximately 1 to 5% by weight of the total composition.

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16. Composition according to any one of claims 1 to 15, which is in the form of a pseudo-emulsion, an oil-in-water emulsion, a water-in-oil emulsion, a water-in-silicon fluid emulsion, a gel, or a water-in-oil-in-water multiple emulsion.

17. Composition according to claim 16, which is in the form of a pseudo-emulsion or an oil-in-water emulsion.

18. Composition according to any one of claims 1 to 7 adapted for local or topical application.

19. Use of a composition according to any one of claims 1 to 17 as a medicament intended for the treatment of the symptoms of hypersensitivity and cutaneous intolerance, for the treatment of the symptoms of psoriasis, for treatment of the symptoms of atopy, for the treatment of the symptoms of acne, for the treatment of the symptoms of cutaneous ageing, or for the prevention of the symptoms of benign estival light eruption.

20. Use of a composition according to any one of claims 1 to 17 for the preparation of a medicament intended for the treatment of the symptoms of hypersensitivity and cutaneous intolerance, for the treatment of the symptoms of psoriasis, for treatment of the symptoms of atopy, for the treatment of the symptoms of acne, for the treatment of the symptoms of cutaneous ageing, or for the prevention of the symptoms of benign estival light eruption.

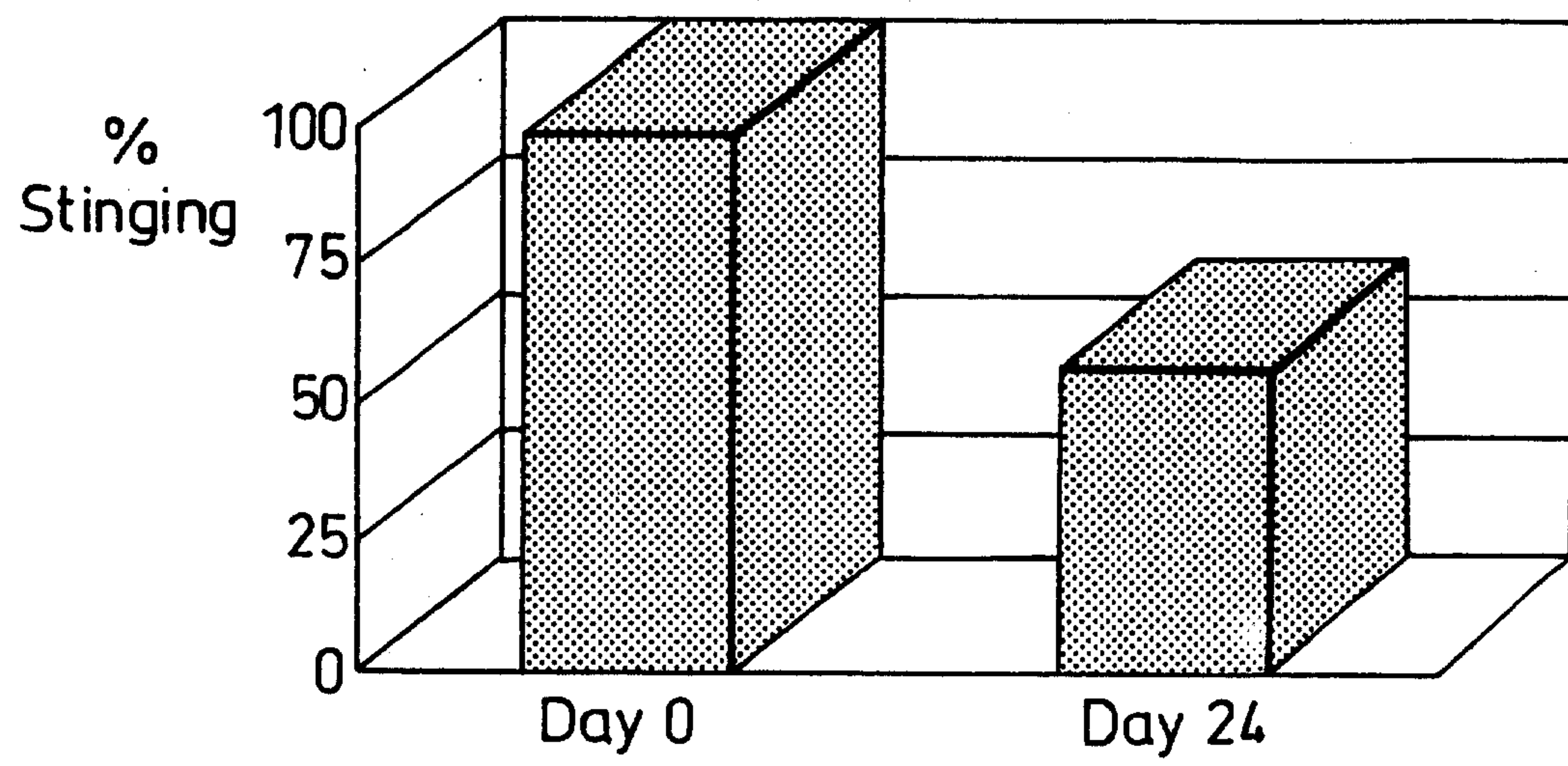


Fig.1