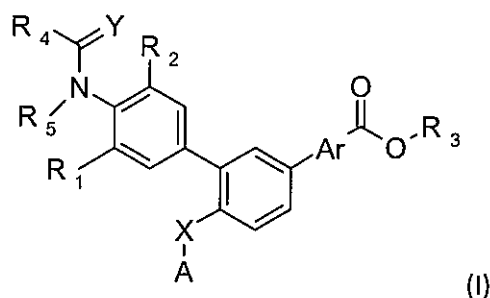


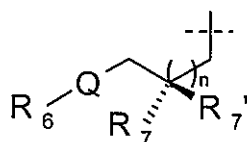
Oil/water-emulsion-type topical compositions containing a retinoid

The invention relates to a composition in the form of emulsion comprising, in a physiologically acceptable environment, at least one new retinoid with the general formula (I)



where:

- R_1 is a hydrogen atom, an alkyl radical of 1 to 4 carbon atoms or a $-CF_3$ radical;
- R_2 is a hydrogen atom, an alkyl or alkoxy radical of 1 to 4 carbon atoms or a chlorine atom;
- R_3 is a hydrogen atom, or a linear or branched alkyl or alkoxy radical of 1 to 10 carbon atoms possibly substituted by a methoxy group;
- R_4 is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- R_5 is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- or R_4 and R_5 together form, with the $-N-C(=Y)-$ bond, a ring of the pyrrolidine, pyrrolidinone, piperidine or piperidinone type;
- Y denotes two hydrogen atoms or a heteroatom such as oxygen or sulfur;
- Ar denotes a 1,4-phenyl, 2,5-pyridyl, 5,2-pyridyl or 2,5-thiophenyl ring;
- X denotes an oxygen atom, possibly substituted by an alkyl or alkylamine chain or a single C-C bond;
- A denotes a hydrogen atom or the following formula:



where

- o Q is an oxygen atom or the bond $-NH-$;
- o R_6 denotes a hydrogen atom, an alkyl radical of 1 to 6 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms, a $-C(O)CH_2$ or $-C(O)CH_2CH_3$ radical;

- R_7 and R_7' denote, independently of each other, a hydrogen atom or a hydroxyl group, on condition that R_7 and R_7' are not simultaneously a hydroxyl group;

n is equal to 0, 1, 2, 3, 4 or 5.

These compounds, described in patent EP1831149, are potent retinoids modulating the nuclear receptor of retinoic acid (RAR), more specifically of the gamma subtype of this receptor (RAR γ).

The receptors RARs activate the transcription by binding with elements of DNA sequences, called the RAR Element (RARE) response elements, in the form of a heterodimer with the X receptors of the retinoids (called RXRs).

Three subtypes of human RARs have been identified and described: RAR α , RAR β and RAR γ .

Since the gamma RAR receptors are located in the epidermis it is important for the compounds described in the general formula (I) to be released in this part of the skin to provide clinical efficacy.

The topical application of retinoids may result in irritation of the skin, dryness and erythema. Numerous articles describe this irritating effect, such as the articles by Stücker & al. *Skin Res Technol.* 2002 May;8(2):133-40 or by Thielitz & al. *Am J Clin Dermatol.* 2008;9(6):369-81.

To obtain topical preparations for pharmaceutical use containing retinoids, numerous techniques are used, in particular emulsions such as those referred to in the patent EP-826366, which describes emulsions which may contain retinoids, or even patent EP-989846, which describes emulsions containing retinoids and at least one emulsifier.

Emulsifiers are molecules that belong to the chemical family of amphiphilic molecules, which are often irritating. Compositions without emulsifiers are in fact less irritating than those containing them.

The fact that emulsifiers are not used in the compositions containing retinoids would therefore enable cutaneous irritation due to the presence of this class of molecule to be limited.

The prior art describes O/W emulsions with or without emulsifier. We may cite, in particular, patent US 5,851,538, which describes formulations with or without emulsifier with porous microspheres containing a practically continuous network of pores open to the outside and comprising retinoids.

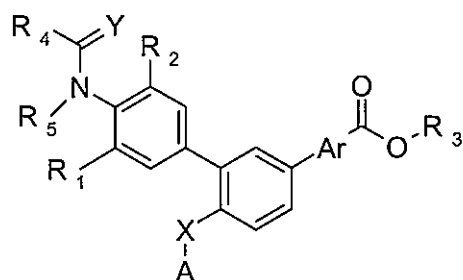
Nevertheless, although the compounds described by the general formula (I) exhibit interesting chemical and physical stability properties for preparations for pharmaceutical uses, they degrade chemically in many of their solvents.

There is therefore a need for stable, well tolerated pharmaceutical compositions containing compounds described by general formula (I).

A first subject according to the invention relates to an oil-in-water emulsion-type composition comprising

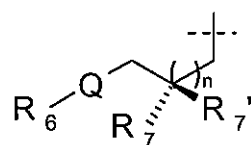
- a fatty phase comprising:

a compound with general formula (I)



where:

- R₁ is a hydrogen atom, an alkyl radical of 1 to 4 carbon atoms or a -CF₃ radical;
- R₂ is a hydrogen atom, an alkyl or alkoxy radical of 1 to 4 carbon atoms or a chlorine atom;
- R₃ is a hydrogen atom, or a linear or branched alkyl or alkoxy radical of 1 to 10 carbon atoms possibly substituted by a methoxy group;
- R₄ is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- R₅ is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- or R₄ and R₅ together form, with the -N-C(=Y)- bond, a ring of the pyrrolidine, pyrrolidinone, piperidine or piperidinone type;
- Y denotes two hydrogen atoms or a heteroatom such as oxygen or sulfur;
- Ar denotes a 1,4-phenyl, 2,5-pyridyl, 5,2-pyridyl or 2,5-thiophenyl ring;
- X denotes an oxygen atom, possibly substituted by an alkyl or alkylamine chain or a single C-C bond;
- A denotes a hydrogen atom or the following formula:



where:

- o Q is an oxygen atom or the bond -NH-;
- o R₆ denotes a hydrogen atom, an alkyl radical of 1 to 6 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms, a -C(O)CH₂ or -C(O)CH₂CH₃ radical;

- R_7 and R_7' denote, independently of each other, a hydrogen atom or a hydroxyl group, on condition that R_7 and R_7' are not simultaneously a hydroxyl group;

n is equal to 0, 1, 2, 3, 4 or 5 ;

at least one principal solvent of the compound (I) and at least one co-solvent oil of the compound (I), and

- an aqueous phase comprising at least one gelifying agent.

A second subject according to the invention relates to a composition such as described above for its use as a medicinal product.

A third subject according to the invention relates to a composition as described above for its use in the treatment of pathologies such as:

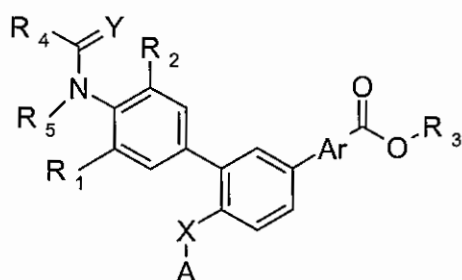
- 1) dermatological complaints associated with a keratinisation disorder relating to cellular differentiation and proliferation, particularly for treating common acnes, comedonic acnes, polymorphic acnes, rosacea acnes, nodulocystic acnes, conglobata acne, senile acnes and secondary acnes such as solar, medicamentous or professional acne;
- 2) keratinisation disorders, in particular ichthyoses, ichthyosiform conditions, lamellar ichthyosis, Darrier's disease, palmoplantar keratodermias, leukoplasias, pityriasis rubra pilaris and leukoplasiform conditions, cutaneous or mucous (oral) lichen;
- 3) dermatological disorders with an inflammatory immune-allergic component, with or without cellular proliferation disorder, and in particular all forms of psoriasis, whether cutaneous, mucous or ungueal, and even psoriatic rheumatism, or atypical dermatitis and the different forms of eczema;
- 4) cutaneous disorders due to exposure to UV radiation, as well as to repair or control ageing of the skin, whether photo-induced or chronological, or to reduce pigmentations and actinic keratoses, or all pathologies associated with chronological or actinic ageing, such as xerosis, pigmentations and wrinkles;
- 5) Any condition associated with benign dermal or epidermal proliferations, whether or not of viral origin, such as common warts, flat warts, molluscum contagiosum and verruciform epidermodysplasia, oral or florid papillomatoses;
- 6) dermatological complaints such as immune dermatoses such as erythematous lupus, bullous immune diseases and collagenic diseases such as sclerodermia;

- 7) stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;
- 8) healing complaints, or to prevent or repair stretch marks, or else to promote healing;
- 9) any disorder of fungal origin in the cutaneous region, such as tinea pedis and tinea versicolor;
- 10) pigmentation disorders such as hyperpigmentation, melasma, hypopigmentation or vitiligo ;
- 11) cancerous or pre-cancerous, cutaneous or mucous conditions such as actinic keratoses, Bowen's disease, carcinomas in-situ, keratoacanthoma and skin cancers such as basocellular carcinoma (BCC), spinocellular carcinoma (SCC) and cutaneous lymphomas such as T lymphoma.

A fourth subject according to the invention relates to a method for preparing an oil-in-water emulsion-type composition as described above and comprising the following stages:

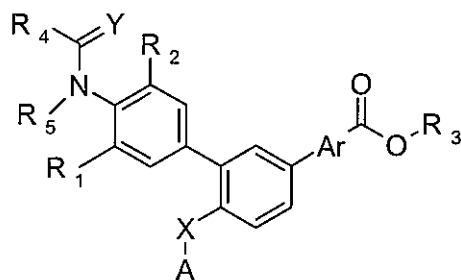
- a) solubilisation of the hydrophilic excipients under agitation
- b) solubilisation under agitation of the retinoid in the principal solvent
- c) addition of the lipophilic excipients
- d) gelification of the aqueous phase by adding the gelifier
- e) addition of the oily phase, then the silicone oil.

A fifth object according to the invention relates to the compositions comprising a compound with general formula (I)



And at least one polyacrylamide gelifier, characterised in that the maximum quantity of active ingredient absorbed in the epidermis 16 hours after application is between 6 ng/cm² and 19 ng/cm².

A sixth object according to the invention relates to the oil-in-water emulsion-type compositions comprising a compound with general formula (I)



And at least one polyacrylamide gelifier, characterised in that the maximum quantity of active ingredient absorbed in the epidermis is obtained between 3 and 10 hours after application and preferably between 5 and 7 hours after application.

The invention will be described in greater detail in the description and the examples which follow, and also in the appended figures in which:

Figure 1 presents the distribution profile in the various compartments of the skin of a composition according to the invention.

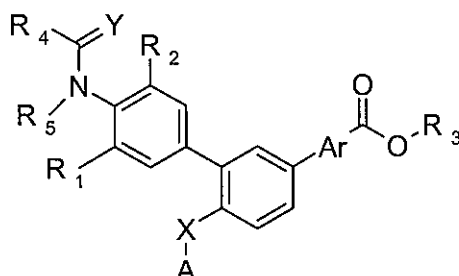
Figure 2 presents the kinetics of penetration into the epidermis of a composition according to the invention.

Figure 3 presents the results of a study of tolerance of a composition according to the invention, compared with a reference gel.

Detailed description of the invention

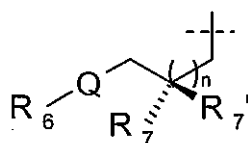
To facilitate the reading of this description reference will be made to general formula (I) and compound A in the remaining text, as being described thus:

General formula (I) :



where:

- R_1 is a hydrogen atom, an alkyl radical of 1 to 4 carbon atoms or a $-CF_3$ radical;
- R_2 is a hydrogen atom, an alkyl or alkoxy radical of 1 to 4 carbon atoms or a chlorine atom;
- R_3 is a hydrogen atom, or a linear or branched alkyl or alkoxy radical of 1 to 10 carbon atoms optionally substituted by a methoxy group;
- R_4 is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- R_5 is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- or R_4 and R_5 together form, with the $-N-C(=Y)-$ bond, a ring of the pyrrolidine, pyrrolidinone, piperidine or piperidinone type;
- Y denotes two hydrogen atoms or a heteroatom such as oxygen or sulfur;
- Ar denotes a 1,4-phenyl, 2,5-pyridyl, 5,2-pyridyl or 2,5-thiophenyl ring;
- X denotes an oxygen atom, possibly substituted by an alkyl or alkylamine chain or a single C-C bond;
- A denotes a hydrogen atom or the following formula:



where

- Q is an oxygen atom or the bond $-NH-$;
- R_6 denotes a hydrogen atom, an alkyl radical of 1 to 6 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms, a $-C(O)CH_2$ or $-C(O)CH_2CH_3$ radical;

- R_7 and R_7' denote, independently of each other, a hydrogen atom or a hydroxyl group, on condition that R_7 and R_7' are not simultaneously a hydroxyl group;

n is equal to 0, 1, 2, 3, 4 or 5.

Compound A: as being 3''-tert-butyl-4'-(2-hydroxy-ethoxy)-4''-pyrrolidin-1-yl-[1,1';3',1'']-terphenyl-4-carboxylic acid.

Due to the physico-chemical characteristics of the active ingredient, the Applicant has had to face a certain number of constraints in the use of the compounds described by general formula (I).

These compounds:

- are soluble in few solvents normally used in the fatty phases of the topical emulsions
- degrade chemically in many of their solvents
- degrade chemically in the presence of numerous emulsifiers.

A first subject according to this invention describes compositions containing at least one compound with general formula (I) in the form of emulsions of the type O/W (Oil in Water) and in which the active ingredient is solubilised in the fatty phase.

According to a particularly preferred embodiment, the composition according to the invention does not contain any emulsifier.

These emulsions exhibit good physical and chemical stability, a rapid rate of penetration and a high level of penetration in the epidermis and/or the dermis.

Emulsion is understood to mean a macroscopically homogeneous but microscopically heterogeneous mixture of two immiscible liquid substances that we shall call phases. An O/W (oil in water) emulsion consists of a fatty (or oily) phase dispersed in an aqueous phase.

In the invention the compositions contain the active ingredient described by general formula (I) at concentrations ranging from 0.00001% to 1% by weight, preferably from 0.0001 to 0.1 % by weight, and more preferably from 0.001 to 0.1 % by weight, relative to the total weight of the composition.

Preferably the active ingredient described by general formula (I) is compound A.

In the invention the compositions contain at least one gelifying agent.

The term "gelifying agent" is intended to mean a polymer compound capable of conferring on the composition the texture of a gel.

The gelifying agent (s) may in particular be selected from polymers of plant origin, gums, pectins, cellulose and its derivatives, polymers of microbiological origin, such as xanthan gum, and gelifying polymers of synthetic origin.

By way of non-exhaustive example of gelifiers that may enter into the compositions, mention may be made of Acrylates/C10-30 Alkyl Acrylate Crosspolymer, sold under the name of Pemulen TR-1 or Pemulen TR-2 by the company Lubrizol, gelifiers in the polyacrylamide family, such as the mixture of Sodium acrylamide/acryloyldimethyltaurate copolymer / isohehexadecane / polysorbate 80, sold under the name of Simulgel 600PHA by the company SEPPIC, and the mixture of polyacrylamide/isoparaffin C13-14/laureth-7 sold under the name of Sepigel 305 by the company SEPPIC,

the carbomers sold under the name of Ultrez 20®, Ultrez 10®, Carbopol 1382® or Carbopol ETD2020NF®, Carbopol 981 or even Carbopol 980 by the company Lubrizol, the polysaccharides with, by way of non-exhaustive examples, xanthan gum, such as Xantural180® sold by the company Kelco, gellan gum sold under the name of Kelcogel by the company Kelco, guar gum, cellulose and its derivatives, such as microcrystalline cellulose and carboxymethyl cellulose of sodium sold under the name of Avicel CL-611 by the company FMC Biopolymer, hydroxypropylmethylcellulose, in particular the product sold under the name of Methocel E4M premium by the company Dow Chemical, or hydroxyethylcellulose, in particular the product sold under the name of Natrosol HHX 250® by the company Ashland, sodium carboxymethylcellulose, in particular Blanose cellulose gum 7F sold by the company Ashland, the family of aluminium magnesium silicates, such as Veegum K sold by the company Vanderbilt, the family of acrylic polymers coupled to hydrophobic chains such as PEG-150/decyl/SMDI copolymer sold under the name of Aculyn 44 (polycondensate, comprising, at least as elements, a polyethylene glycol with 150 or 180 mols of ethylene oxide, decyclic alcohol and methylene bis(4-cyclohexylisocyanate) (SMDI), at 35% by weight in a mixture of propylene glycol (39%) and water (26%)), the family of modified starches such as modified potato starch sold under the name of Structure Solanacée or their mixtures, the family of the carrageenans, particularly those distributed among four major families: κ , λ , β , ω , such as Viscarin® and the Gelcarin® marketed by the company IMCD.

Preferably a gelifying agent of the polyacrylamide type, such as Simulgel 600 PHA®, which has thickening and stabilising properties, is used in concentrations ranging from 0.005 to 5 % by weight, and preferably ranging from 1% to 4% by weight.

The person skilled in the art knows that for an emulsifier system the proportion of emulsifier required to emulsify a fatty phase in an oil in water emulsion is normally of the order of 1/5 of the % of the fatty phase. By way of non-exhaustive example a fatty phase representing at least 11% of the ingredients of the formulas would require a minimum of 2.2% of emulsifiers.

According to a preferred embodiment of the invention, no emulsifier is used. However, it is possible in spite of this that certain ingredients contain low percentages of emulsifier in their own composition. Because of the low percentage that may result from this in the composition according

to the invention, they cannot have the function of an emulsifier in the composition (content preferably lower than 0.6% by weight, relative to the total weight of the composition).

In the invention the compositions contain a fatty phase that may consist of:

- a principal solvent of an active ingredient described by general formula (I), which may be in particular benzyl alcohol, laureth-4, phenoxyethanol, propylene glycol monocaprylate, pentyleneglycol or dimethyl isosorbide, and preferably phenoxyethanol sold, for example, under the name phenoxetol by Clariant.

When the principal solvent is phenoxyethanol, the amount of phenoxyethanol ranges from 0.2 to 5% by weight and preferably from 0.5 to 2% by weight relative to the total weight of the composition.

The term "principal solvent" is intended to mean a liquid which has the property of dissolving, diluting or extracting other substances without causing any chemical modification of these substances and without itself being modified.

According to the invention, a principal solvent is such a liquid, in which the compounds with the general formula (I) (and more preferably the compound A) have a solubility, at ambient temperature and atmospheric pressure, greater than or equal to 0.1% by weight.

- one or more co-solvent oils of an active ingredient described by general formula (I), which may be, in preference, chosen from the following co-solvent oils: Caprylic/ capric triglycerides (Miglyol 812N) supplied by IMCD, Prunus Amygdalus Dulcis (Sweet Almond) oil supplied by SICTIA, Propylene glycol monocaprylate (Capryol 90) supplied by GATTEFOSSE, Propylene glycol laurate (Lauroglycol FCC) supplied by GATTEFOSSE, Sorbitan Sesquioleate (Arlacel 83VPharma) supplied by CRODA, Diisopropyl Adipate (Crodamol DA) supplied by CRODA, PPG-15 stearyl ether (Arlamol PS15E-LQ) supplied by CRODA, Apricot Kernel Oil PEG-6 Ester (Labrafil M1944CS) supplied by GATTEFOSSE in proportions which can range from 0.5 to 50% by weight and preferably from 4 to 30% by weight.

The term "co-solvent" is intended to mean a substance having the role of solvent in combination with another substance.

In the invention the compositions described above may also contain additives (among which mention may be made of the following categories, used alone or in combination):

- One or more silicone oils that improve the properties of the formula on application, such as Cyclomethicone (St-Cyclomethicone 5NF) or Dimethicone (Q7 9120 silicon fluid, with a viscosity of 20 cst to 12500 cst from Dow Corning) between 0 and 10%, and preferably between 0 and 4%.

- One or more preservatives such as methyl parabene, propyl parabene, benzalconium chloride, phenoxyethanol sold under the name of phenoxetol by Clariant, benzyl alcohol sold

under the name benzyl alcohol by Merck, potassium sorbate sold under the name of potassium Sorbate by VWR, benzoic acid sold under the name Benzoic Acid by VWR, 2-Bromo-2-Nitropropane-1,3-Diol sold under the name of Bronopol by Jan Dekker International, Chlorohexidine sold under the name of Chlorohexidine digluconate 20% solution by Arnaud Pharmacie, chlorocresol and its derivatives, sodium benzoate sold under the name of Probenz SP by the company Unipex, ethyl alcohol and diazolidinyl urea. These preservatives may be used alone or in combination for effective protection of formulas against all bacterial contamination in contents ranging from 0% to 5% by weight, and preferably from 0.01 to 2% by weight.

The term "preservative" denotes any substance capable of opposing the modifications of chemical or microbiological origin of a product.

- Ethanol, the quantity of which may be between 0 and 30% by weight and preferably between 0 and 10% by weight.

- Moistening agents, preferably polyols and preferably selected from among propylene glycol, glycerine, diglycerine or sorbitol (Neosorb supplied by ROQUETTE, Parteck SI supplied by Merck, but also Sorbitol USP Powder supplied by LIPO CHEMICALS), whose quantity ranges from 0 to 40% by weight relative to the total weight of the composition, and preferably from 5 to 35%.

- Chelating agents such as EDTA (ethylene diamine tetraacetic acid) and its derivatives or salts, dihydroglycerine, citric and tartaric acids, gluconolactone sold under the name glucono-delta-lactone SG by Jungbunzlauer or mixtures thereof.

- Antioxidants such as vitamin E and its derivatives, such as DL alpha tocopherol or tocopherol acetate from Roche; vitamin C and its derivatives, such as Ascorbyl Palmitate from Roche, Butylhydroxy toluene sold under the name of Nipanox BHT by Clariant.

- Palliatives and/or anti-irritants such as PPG-12/SMDI copolymer sold by Bertek Pharmaceuticals under the commercial name of Polyolprepolymer-2, glycyrrhetic acid or its derivatives, for example Enoxolone sold by the company BASF, hyaluronic acid as such or in its form of sodium hyaluronate sold under the commercial name of HYAL. NA PWD PH 15-51-45 by the company Contipro, allantoin sold under the name of RONACARE ALLANTOINE by MERCK.

- Any other additive normally used in the pharmaceutical and cosmetic fields enabling specific properties to be assigned to the said preparation.

GENERAL COMPOSITION FOR ACNE:

When it is intended for the treatment of acne, the composition according to the invention advantageously contains the following ingredients, the percentages being expressed by weight in relation to the total weight of the composition of the oil in water emulsion type.

- from 0.00001% to 1% and preferably from 0.0001 to 0.1 % of compound with the general formula (I)
- from 0.005 to 10 % and preferably from 1 to 5% of gelifier
- from 0.2 to 5% and preferably from 0.5 to 2% of principal solvent of the compound with the general formula (I)
- from 0.5 to 50% and preferably from 4 to 15% of co-solvent oils of the compound with the general formula (I)
- from 0 to 20% and preferably from 0 to 5% of mineral oils
- from 0 to 50% and preferably from 5 to 35% of polyol
- from 0 to 10% and preferably from 0 to 4% of silicone oil
- from 0 to 5% and preferably from 0.01 to 2% of preservative system
- from 0 to 30% and preferably from 0 to 10% of ethanol
- from 0 to 15% and preferably from 0.1 to 10% of additives

COMPOSITIONS SUITABLE FOR ICTHYOSIS, PALMOPLANTAR HYPERKERATOSIS OR PSORIASIS:

In this case, the composition according to the invention advantageously contains the following ingredients, the percentages being expressed by weight in relation to the total weight of the composition of the oil-in-water emulsion type.

- from 0.00001% to 1% and preferably from 0.0001 to 0.1% of compound with the general formula (I)
- from 0.005 to 10 % and preferably from 1 to 5% of gelifier
- from 0.2 to 5% and preferably from 0.5 to 2% of principal solvent of the compound with the general formula (I)
- from 0.5 to 50% and preferably from 10 to 30% of co-solvent oils of the compound with the general formula (I)
- from 1 to 50% and preferably from 10 to 30% of polyol
- from 0 to 10% and preferably from 0 to 4% of silicone oil
- from 0 to 5% and preferably from 0.01 to 2% of preservative system
- from 0 to 15% and preferably from 0.1 to 10% of additives

Another object according to the invention relates to a method of preparing a composition described as above and comprising the following stages:

A) Preparation of the aqueous phase

Solubilisation of the hydrophilic excipients under agitation, if necessary under heat

B) Preparation of the oily phase

In a suitable receptacle, solubilisation under agitation, of compound A in Phenoxyethanol, under heat if necessary.

Allow to return to ambient temperature and add the lipophilic excipients except the silicone oil (for example ST-cyclomethicone 5) when this is present.

C) Mixing of the two phases.

At ambient temperature gelify the aqueous phase by adding the gelifier (for example Simulgel 600PHA), then add the oily phase then the silicone oil when this is present.

Examples

Example 1 – Pre-formulation

In order to obtain an oil in water emulsion containing a compound with the general formula (I) in the fat phase, pre-formulation studies have been conducted to identify the excipients allowing good solubilisation as well as good stability of the active ingredient.

(1) List of fat phase excipients in which the maximum solubility has been determined by HPLC :

Excipients		Maximum solubility
Commercial name	INCI name	%
Benzyl alcohol	Benzyl Alcohol	2.388
Brij 30	Laureth-4	2.03
Phenoxetol	Phenoxyethanol	1.957
Capryol 90	Propylene glycol monocaprylate	0.802
Hydrolite 5P	Pentylene glycol	0.482
Arlasolve DMI	Dimethyl Isosorbide	0.400
Crodamol IPM	Isopropyl myristate	< 0.1

The limit below which the compounds with the general formula (I) are considered as being not solubilised is 0.1% by weight.

- (2) Stability of compound A in its principal solvents:

These stability studies of compound A in its principal solvents show that compound A degrades chemically in a number of its solvents.

These results have enabled us to select our principal solvent (phenoxyethanol) and our co-solvent oils from among the solvent oils which exhibit good stability results, with the aim of developing O/W emulsions in which compound A is solubilised in the oily phase.

Excipients		COMPOUND A	Stability results
Commercial name	INCI name	%	
Miglyol 812N	Caprylic/ capric triglycerides	0.005%	Stable/ Ok 6Months 40°C
Sweet almond oil	Prunus Amygdalus Dulcis (Sweet Almond) Oil	0.005%	Stable/ Ok 6Months 40°C
Capryol 90	Propylene glycol monocaprylate	0.05%	Stable/ Ok 6Months 40°C

Arlacel 83V Pharma	Sorbitan Sesquioleate	0.05%	Stable/ Ok 6Months 40°C
Crodamol DA	Diisopropyl Adipate	0.05%	Stable/ Ok 6Months 40°C
Lauroglycol FCC	Propylene glycol laurate	0.05%	Stable/ Ok 6Months 40°C
Arlamol PS15E-LQ	PPG-15 stearyl ether	0.05%	Stable/ Ok 6Months 40°C
Phenoxetol	Phenoxyethanol	0.05%	Stable/ Ok 6Months 40°C
Labrafil M1944CS	Apricot Kernel Oil PEG-6 Ester	0.05%	Stable/ Ok 6Months 40°C
Dipropylene Glycol Care	Dipropylene glycol	0.05%	Unstable
Brij 30	Laureth-4	0.05%	Unstable
Benzyl Alcohol	Benzyl Alcohol	0.05%	Unstable
Eutanol G	Octyldodecanol	0.05%	Unstable
Myritol PC	Propylene glycol dicaprylate/ dicaprinate	0.05%	Unstable
Arlasolve DMI	Dimethyl Isosorbide	0.05%	Unstable
Marcol 152	Paraffinum Liquidum	0.05%	N/A

(3) Stability of compound A in mixtures of excipients (solvent/surfactants) determined by HPLC :

Studies of stability of compound A solubilised in oils (in which it is stable) in the presence of surfactants have been conducted:

Mixture of excipients		COMPOUND A	Stability results
Commercial name	INCI name	%	
Simulsol M45/ Crodamol DA	PEG-8 Stearate/ Diisopropyl Adipate	0,05%	Unstable
Cremophor EL/ Labrafil M1944CS	PEG-35 Castor Oil/ Apricot Kernel Oil PEG-6 Ester	0,05%	Unstable
Tween 80/ Arlamol PS15E-LQ	Polysorbate-80/ PPG-15 stearyl ether	0,05%	Unstable
Cremophor EL/ Lauroglycol FCC	PEG-35 Castor Oil/ Propylene glycol laurate	0,05%	Unstable
Tween 80/ Hexylene glycol	Polysorbate-80/ Hexylene glycol	0,2%	Unstable
Cremophor EL/ Labrafil M1944CS	PEG-35 Castor Oil/ Apricot Kernel Oil PEG-6 Ester	0,2%	Unstable
Cremophor RH40/ Crodamol DA	PEG-40 Hydrogenated Castor Oil/ Diisopropyl Adipate	0,2%	Unstable
Tween 80/ Lauroglycol FCC	Polysorbate-80/ Propylene glycol laurate	0,2%	Unstable
Simulsol M45/ Crodamol DA	PEG-8 Stearate/ Diisopropyl Adipate	0,2%	Unstable
Arlacel 165/ Lauroglycol FCC	Glyceryl Stearate PEG-100 Stearate/ Propylene glycol laurate	0,05%	Unstable
GlucateSS-Glucamate SSE-20/ Arlamol PS15E-LQ	Methyl Glucose Sesquistearate- PEG-20 Methyl Glucose Sesquistearate/ PPG-15 stearyl ether	0,05%	Unstable
Brij 721/ Arlamol PS15E-LQ	Steareth-21/ PPG-15 stearyl ether	0,05%	Stable/ Ok 3Months 40°C
Brij 721/ Lauroglycol FCC	Steareth-21/ Propylene glycol laurate	0,05%	Stable/ Ok 3Months 40°C
Eumulgin B2/ Arlamol E	Ceteareth-20/ PPG-15 stearyl ether	0,05%	Stable/ Ok 3Months 40°C
Arlacel 165/ Arlamol E	Glyceryl Stearate PEG-100 Stearate/ PPG-15 stearyl ether	0,05%	Stable/ Ok 3Months 40°C
GlucateSS-Glucamate SSE-20/ Lauroglycol FCC	Methyl Glucose Sesquistearate- PEG-20 Methyl Glucose Sesquistearate/ Propylene glycol laurate	0,05%	Stable/ Ok 3Months 40°C

The limits fixed for high stability are 95%-105% as a percentage relative to T0.

These studies showed that compound A degrades chemically in the presence of numerous surfactants. Following these results we therefore decided to develop an O/W emulsion without emulsifier.

EXAMPLE 2: Formulations

In the following examples the formulae are characterised at T0. The physical and chemical stability of the formulations is achieved after storage at ambient temperature (TA) and at +40°C after T+1Month and/or T+2Months or T+3Months or T+6Months. The equipment and methods used for these characteristics are described below.

Compound A is defined as 3''-tert-butyl-4'-(2-hydroxy-ethoxy)-4''-pyrrolidin-1-yl-[1,1';3',1'']-terphenyl-4-carboxylic acid.

-Chemical assaying of compound A:

-Equipment: HPLC

-Expression of the results: the titre of the active ingredient is expressed as a % related to the initial % achieved at T0. The limits fixed for high stability are 95%-105%.

-Macroscopic observation:

- Macroscopic observation enables the physical integrity of the products at T0 and after stability to be guaranteed.

-Microscopic observation:

- Microscopic observation enables good solubilisation of compound A from T0, non-recrystallisation in the course of time, as well as the size of the globules in the oily phase to be evaluated.

-Equipment: AXIO ZEISS Microscope

-pH:

-Equipment: METTLER TOLEDO Seven Multi pH meter

-Method : Measurements carried out at ambient temperature after 24h stabilisation in an enclosure at 25°C of all the samples.

-Viscosity:

-The measurement of the viscosity enables the consistency of the formulas produced to be evaluated.

-Equipment: Brookfield RV DVII + Pro

-Method: Measurements carried out at ambient temperature after 24h stabilisation in an enclosure at 25°C of all the samples. The value is read after 1 minute. The choice of spindle and speed will be described in each composition example. The values obtained are expressed in centipoises (Cps).

-Centrifuging:

-The centrifuging enables the resistance of the formulas to a mechanical stress to be evaluated.

-Equipment: Galaxy 14D VWR

-Method: 30 minutes at 5000 rpm

-A conforming result means that there is neither separation of phases nor exudate.

Formula 1

COMMERCIAL NAME			INCI NAME			%				
COMPOUND A			COMPOUND A			0.010				
PROPYLENE GLYCOL			Propylene Glycol			30.000				
ETHANOL 95-96%			Ethanol			5.000				
RONACARE ALLANTOIN			Allantoin			0,200				
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80			3.000				
MIGLYOL 812 N			Medium-Chain Triglycerides			8.000				
ST-CYCLOMETHICONE 5-NF			Cyclopentasiloxane			2.000				
PHENOXYTOL			Phenoxyethanol			1.000				
PURIFIED WATER			Purified water			QS 100.000				
CHARACTERISATION AT 20			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream					
			MICROSCOPIC APPEARANCE		Absence of crystals. Very fine, homogeneous emulsion. Ø < 5 µm : 90%					
			pH		5					
			VISCOSITY		Needle 6, Rate 5. 176 000cP					
			CENTRIFUGING		Conforming					
STABILITY MONITORING			1 Month		2 Months		3 Months		6 Months	
Physical stability	pH TA/ 40°C		5.28 / 5.31		5.45 / 5.81		5.30 / 5.67		5.23 / 5.75	
	Viscosity	AT	169 000cP		166 000cP		175 000cP		172 000cP	
		40°C	174 000cP		173 000cP		165 000cP		159 000cP	
Chemical stability	Dose COMPOUND A initial %	AT	98.70		100.40		100.30		103.10	
		40°C	99.40		101.30		98.80		104.90	

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 2

COMMERCIAL NAME			INCI NAME			%
COMPOUND A			COMPOUND A			0.005
PROPYLENE GLYCOL			Propylene Glycol			30.000
ETHANOL 95-96%			Ethanol			5.000
RONACARE ALLANTOIN			Allantoin			0.200
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80			3.000
MIGLYOL 812 N			Medium-Chain Triglycerides			8.000
ST-CYCLOMETHICONE 5			Cyclopentasiloxane			2.000
PHENOXTOL			Phenoxyethanol			1.000
PURIFIED WATER			Purified water			QS 100.000
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Very fine, homogeneous emulsion. Ø < 5 µm: 90%	
			pH		5	
			VISCOSITY		176 000cP	
			CENTRIFUGING		Conforming	
Chemical stability	Dose COMPOUND A initial %	AT	100.60	100.20	98.00	100.50
		40°C	99.40	100.40	96.80	96.60

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 3

COMMERCIAL NAME			INCI NAME		%	
COMPOUND A			COMPOUND A		0.010	
PROPYLENE GLYCOL			Propylene Glycol		30.000	
BLANOSE CELLULOSE GUM 7H4F			Cellulose Gum		0.800	
ETHANOL 95-96%			Ethanol		5.000	
RONACARE ALLANTOIN			Allantoin		0.200	
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80		2.000	
MIGLYOL 812 N			Triglycerides Medium-Chain		8.000	
ST-CYCLOMETHICONE 5			Cyclopentasiloxane		2.000	
PHENOXYTOL			Phenoxyethanol		1.000	
PURIFIED WATER			Purified water		QS	100.00
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Very fine, homogeneous emulsion. Ø < 5 µm : 90%	
			pH		6,36	
			VISCOSITY		Needle 6, Rate 10. 57 500cP	
			CENTRIFUGING		NR	
STABILITY MONITORING			1 Month	2 Months	3 Months	6 Months
Physical stability	pH AT/ 40°C		6.61 / 6.31	6,37 / 6.21	6.48 / 6.18	6.40 / 6.08
	Viscosity	AT	64 500cP	59 800cP	67 000cP	64 600cP
		40°C	59 000cP	59 000cP	55 100cP	57 300cP
Chemical stability	Dose COMPOUND A Initial %	AT	104.00	100.5	100.00	95.00
		40°C	104.8	100.00	99.60	94.70

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 4

COMMERCIAL NAME			INCI NAME		%	
COMPOUND A			COMPOUND A		0.010	
PROPANEDIOL-1,2			Propylene Glycol		30.000	
ETHANOL 95-96%			Ethanol		5.000	
RONACARE ALLANTOIN			Allantoin		0, 200	
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80		3.000	
MIGLYOL 812 N			Caprylic/Capric Triglyceride		8.000	
LABRAFIL M1944CS			Apricot Kernel Oil PEG-6 Ester		2.000	
ST-CYCLOMETHICONE 5			Cyclopentasiloxane		2.000	
PHENOXYTOL			Phenoxyethanol		1.000	
PURIFIED WATER			Purified water		QS 100.000	
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Very fine, homogeneous emulsion. Ø < 5 µm : 90%	
			pH		4,72	
			VISCOSITY		Needle 6, Rate 2.5. 215 000 cP	
			CENTRIFUGING		NR	
STABILITY MONITORING			1 Month	2 Months	3 Months	6 Months
Physical stability	pH AT/ 40°C		NR / 5.58	NR / 5.47	NR / 5.53	NR / NR
	Viscosity	AT	NR	NR	NR	NR
		40°C	183 000cP	168 000cP	158 000cP	NR
Chemical stability	Dose COMPOUND A Initial %	AT	1.5 Months: 99.90		99.90	NR
		40°C	1.5 Months: 99.00		99.40	NR

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 5

COMMERCIAL NAME			INCI NAME		%	
COMPOUND A			COMPOUND A		0.010	
PROPANEDIOL-1,2			Propylene Glycol		30.000	
ETHANOL 95-96%			Ethanol		5.000	
RONACARE ALLANTOIN			Allantoin		0.200	
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80		3.000	
MIGLYOL 812 N			Caprylic/Capric Triglyceride		8.000	
ARLAMOL PS15E-LQ (WL)			PPG-15 stearyl ether		2.000	
ST-CYCLOMETHICONE 5-NF			Cyclopentasiloxane		2.000	
PHENOXETOL			Phenoxyethanol		1.000	
PURIFIED WATER			Purified water		QS 100.000	
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Fine, homogeneous emulsion. Ø < 10 µm : 90%	
			pH		4,64	
			VISCOSITY		Needle 6, Rate 2,5. 314 000 cP	
			CENTRIFUGING		NR	
STABILITY MONITORING			1 Month	2 Months	3 Months	6 Months
Physical stability	pH AT/ 40°C		NR / 5.62	NR / 5.68	NR / 5.65	NR / 5.81
	Viscosity	AT	NR	NR	NR	NR
		40°C	267 000cP	268 000cP	262 000cP	246 000cP
Chemical stability	Dose COMPOUND A Initial %	AT	1.5 Months: 98.80		100.70	107.00
		40°C	1.5 Months: 106.00		100.70	107.70

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 6

COMMERCIAL NAME			INCI NAME		%	
COMPOUND A			COMPOUND A		0.030	
PROPANEDIOL-1,2			Propylene Glycol		30.000	
ETHANOL 95-96%			Ethanol		5.000	
RONACARE ALLANTOIN			Allantoin		0.200	
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80		3.000	
ST-CYCLOMETHICONE 5NF			Cyclopentasiloxane		2.000	
CASTOR OIL PH			Ricinus Communis (Castor) Seed Oil		8.000	
PHENOXYTOL			Phenoxyethanol		1.000	
PURIFIED WATER			Purified water		QS 100.000	
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Fine, homogeneous emulsion. Ø < 5 µm : 90%	
			pH		5,67	
			VISCOSITY		Needle 29, Rate 0.5. 1 180 000 cP	
			CENTRIFUGING		Conforming	
STABILITY MONITORING			1 Month	2 Months	3 Months	6 Months
Physical stability	pH AT/ 40°C		5.66 / 5.55	5.73 / 5.82	5.44 / 5.84	5.44 / 5.84
	Viscosity	AT	1 160 000cP	1 080 000	1 080 000 cP	1 080 000cP
		40°C	1 130 000cP	1 030 000	1 090 000 cP	1 030 000cP
Chemical stability	Dose COMPOUND A Initial %	AT	99.8	100.0	100.4	100.0
		40°C	99.6	99.5	99.2	99.5

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 7

COMMERCIAL NAME			INCI NAME		%	
COMPOUND A			COMPOUND A		0.030	
PROPANEDIOL-1,2			Propylene Glycol		30.000	
ETHANOL 95-96%			Ethanol		5.000	
RONACARE ALLANTOIN			Allantoin		0.200	
SIMULGEL 600 PHA			Acrylamide, AMPS Copolymer Dispersion 40%/ Isohexadecane/ polysorbate 80		3.000	
MIGLYOL 812 N			Caprylic/Capric Triglyceride		4.000	
ARLAMOL PS15E-LQ (WL)			PPG-15 stearyl ether		4.000	
ST-CYCLOMETHICONE 5-NF			Cyclopentasiloxane		2.000	
PHENOXYTOL			Phenoxyethanol		1.000	
PURIFIED WATER			Purified water		QS 100.000	
CHARACTERISATION AT T0			MACROSCOPIC APPEARANCE		White, smooth, brilliant cream	
			MICROSCOPIC APPEARANCE		Absence of crystals. Fine homogeneous emulsion. Ø < 5 µm : 90%	
			pH		5,87	
			VISCOSITY		Needle 29, Rate 5. 139 000 cP	
			CENTRIFUGING		Conforming	
STABILITY MONITORING			1 Month	2 Months	3 Months	6 Months
Physical stability	pH AT/ 40°C		5.90/ 5.50	5.71 / 5.71	5.66/5.90	5.66/5.90
	Viscosity	AT	148 000 cP	132000cP	134 000 cP	132000cP
		40°C	142 000 cP	130000cP	137 000 cP	130000cP
Chemical stability	Dose COMPOUND A Initial %	AT	97.8	109.6	100.7	100.7
		40°C	100.0	110.2	100.6	100.2

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 8

COMPOSITIONS						
Commercial Name		INCI name		%		
COMPOUND A		COMPOUND A		0.010		
PHENOXETOL		PHENOXYETHANOL		1.00		
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		15.00		
CASTOR OIL PH		RICINUS COMMUNIS (CASTOR) SEED OIL		8.00		
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00		
Q7-9120 SILICON FLUID 350 cst		DIMETHICONE		5.00		
RONACARE ALLANTOIN		ALLANTOIN		0.200		
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00		
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		3.00		
PURIFIED WATER		PURIFIED WATER		QS 100.00		
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream			
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø 6 µm			
		pH	4.92			
		VISCOSITY	Needle 6, Rate 0,5 NR			
		CENTRIFUGING	Conforming			
Stability monitoring		1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS	
Physical stability	pH AT/ 40°C		4.92/4.88	NR	4.93/5.22	/
	Viscosity	AT	192.10 ⁴ cp	NR	182. 10 ⁴ cp	/
		40°C	187.10 ⁴ cp	NR	167.10 ⁴ cp	/

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 9

COMPOSITIONS										
Commercial Name		INCI name		%						
COMPOUND A		COMPOUND A		0.010						
PHENOXETOL		PHENOXYETHANOL		1.00						
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		8.00						
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER		15.00						
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00						
RONACARE ALLANTOIN		ALLANTOIN		0.200						
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00						
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		2.5						
PURIFIED WATER		PURIFIED WATER		QS 100.00						
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE		White, smooth, brilliant cream						
		MICROSCOPIC APPEARANCE		Absence of crystals. Fine, homogeneous emulsion. Ø < 7 µm						
		pH		4.79						
		VISCOSITY		Needle 6, Rate 5 187000cp						
		CENTRIFUGING		RAS						
Stability monitoring		1 MONTH		2 MONTHS		3 MONTHS		6 MONTHS		
Physical stability	pH AT/ 40°C		4.76/4.87		4.92/4.99		4.83/5.08		4.59/5.13	
	Viscosity	AT	160000cp		175000cp		186000cp		132000cP	
		40°C	154000cp		146000cp		146000cp		137000cP	

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 10

COMPOSITIONS										
Commercial Name		INCI name		%						
COMPOUND A		COMPOUND A		0.030						
PHENOXETOL		PHENOXYETHANOL		1.00						
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		8.00						
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER		15.00						
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00						
RONACARE ALLANTOIN		ALLANTOIN		0.200						
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00						
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		2.5						
PURIFIED WATER		PURIFIED WATER		QS 100.00						
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE		White, smooth, brilliant cream						
		MICROSCOPIC APPEARANCE		Absence of crystals. Fine, homogeneous emulsion. Ø < 7 µm						
		pH		4.76						
		VISCOSITY		Needle 6, Rate 2.5 381000cp						
		CENTRIFUGING		RAS						
Stability monitoring		1 MONTH		2 MONTHS		3 MONTHS		6 MONTHS		
Physical stability	pH AT/ 40°C		4.74/4.97		4.88/5.00		4.85/5.16		4.96/5.12	
	Viscosity	AT	374000cp		364000cp		334000cp		298000cP	
		40°C	288000cp		266000cp		269000cp		260000cP	

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 11

COMPOSITIONS						
Commercial Name		INCI name		%		
COMPOUND A		COMPOUND A		0.04		
PHENOXETOL		PHENOXYETHANOL		1.00		
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		8.00		
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER		15.00		
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00		
RONACARE ALLANTOIN		ALLANTOIN		0.200		
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00		
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		2.5		
PURIFIED WATER		PURIFIED WATER		QS 100.00		
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream			
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø < 5 µm			
		pH	4.76			
		VISCOSITY	Needle 6, Rate 2,5 340000cp			
		CENTRIFUGING	RAS			
Stability monitoring		1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS	
Physical stability	pH AT/ 40°C		4.77/4.90	4.92/5.02	5.20/5.15	/
	Viscosity	AT	343000cp	330000cp	325000cp	/
		40°C	292000cp	263000cp	271000cp	/

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 12

COMPOSITIONS						
Commercial Name		INCI name		%		
COMPOUND A		COMPOUND A		0.05		
PHENOXETOL		PHENOXYETHANOL		1.00		
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		8.00		
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER		15.00		
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00		
RONACARE ALLANTOIN		ALLANTOIN		0.200		
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00		
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		2.50		
PURIFIED WATER		PURIFIED WATER		QS 100.00		
CHARACTERISATION TO T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream			
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø < 6 µm			
		pH	4.92			
		VISCOSITY	Needle 6, Rate 2,5 363000cp			
		CENTRIFUGING	RAS			
Stability monitoring		1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS	
Physical stability	pH AT/ 40°C		4.93/4.88	4.79/4.93	4.87/5.12	/
	Viscosity	AT	334000cp	356000cp	346000cp	/
		40°C	298000cp	282000cp	275000cp	/

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 13

COMPOSITIONS						
Commercial Name		INCI name		%		
COMPOUND A		COMPOUND A		0.01		
PHENOXETOL		PHENOXYETHANOL		1.00		
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES		8.00		
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER		15.00		
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE		2.00		
RONACARE ALLANTOIN		ALLANTOIN		0.200		
GLYCERINE 4810 VEGETABLE		GLYCERIN		20.00		
SIMULGEL 600 PHA		ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80		3.00		
BENZYL ALCOHOL		BENZYL ALCOHOL		0.40		
POTASSIUM SORBATE		POTASSIUM SORBATE		0.10		
PURIFIED WATER		PURIFIED WATER		QS 100.00		
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream			
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø < 5 µm			
		pH	6.64			
		VISCOSITY	Needle 6, Rate 5 147000cp			
		CENTRIFUGING	RAS			
Stability monitoring		1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS	
Physical stability	pH AT/ 40°C		6.37/6.36	6.60/6.22	6.40/6.13	/
	Viscosity	AT	160000cp	157000cp	121000cp	/

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 14

COMPOSITIONS					
Commercial Name		INCI name	%		
COMPOUND A		COMPOUND A	0.01		
PHENOXETOL		PHENOXYETHANOL	1.00		
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00		
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER	15.00		
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE	2.00		
RONACARE ALLANTOIN		ALLANTOIN	0.200		
GLYCERINE 4810 VEGETABLE		GLYCERIN	20.00		
SIMULGEL 600 PHA		ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	3.00		
SODIUM BENZOATE		SODIUM BENZOATE	0.20		
GLUCONO-DELTA-LACTONE SG		GLUCONOLACTONE	0.25		
PURIFIED WATER		PURIFIED WATER	QS 100.00		
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream		
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø < 8 µm		
		pH	5.44		
		VISCOSITY	Needle 6, Rate 20 36450cp		
		CENTRIFUGING	RAS		
Stability monitoring		1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS
Physical stability	pH AT/ 40°C	4.59/4.58	4.70/4.78	NR	NR

These results demonstrate a good physical stability of the composition as a whole over time.

Formula 15

COMPOSITIONS		
Commercial Name	INCI name	%
COMPOUND A	COMPOUND A	0.01
PHENOXETOL	PHENOXYETHANOL	1.00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15.00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2.00
RONACARE ALLANTOIN	ALLANTOIN	0.200
GLYCERINE 4810 VEGETABLE	GLYCERIN	20.00
SIMULGEL 600 PHA	ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	3.00
BENZYL ALCOHOL	BENZYL ALCOHOL	0.80
POTASSIUM SORBATE	POTASSIUM SORBATE	0.20
TITRIplex III	DISODIUM EDTA	0.10
PURIFIED WATER	PURIFIED WATER	QS 100.00
CHARACTERISATION AT T0	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. $\varnothing < 6 \mu\text{m}$
	pH	6.34
	VISCOSITY	Needle 5, Rate 5 67920cp
	CENTRIFUGING	RAS

Formula 16

COMPOSITIONS		
Commercial Name	INCI name	%
COMPOUND A	COMPOUND A	0.01
PHENOXETOL	PHENOXYETHANOL	1.00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15.00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2.00
RONACARE ALLANTOIN	ALLANTOIN	0.200
GLYCERINE 4810 VEGETABLE	GLYCERIN	20.00
SIMULGEL 600 PHA	ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	3.00
BENZOIC ACID	BENZOIC ACID	0.20
POTASSIUM SORBATE	POTASSIUM SORBATE	0.20
TITRIPLEX III	DISODIUM EDTA	0.10
PURIFIED WATER	PURIFIED WATER	QS 100.00
CHARACTERISATION AT T0	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. $\varnothing < 10\mu\text{m}$
	pH	5.43
	VISCOSITY	Needle 5, Rate 5 59520cp
	CENTRIFUGING	RAS

Formula 17

COMPOSITIONS						
Commercial Name		INCI name	%			
COMPOUND A		COMPOUND A	0.01			
PHENOXETOL		PHENOXYETHANOL	1.00			
MIGLYOL 812N		CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00			
ARLAMOL PS15E-LQ		PPG-15 STEARYL ETHER	15.00			
ST-CYCLOMETHICONE 5NF		CYCLOPENTASILOXANE	2.00			
RONACARE ALLANTOIN		ALLANTOIN	0.200			
GLYCERINE 4810 VEGETABLE		GLYCERIN	20.00			
SIMULGEL 600 PHA		ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	2.5			
BENZALKONIUM CHLORIDE		BENZALKONIUM CHLORIDE	0.05			
PURIFIED WATER		PURIFIED WATER	5.00			
POTASSIUM SORBATE		POTASSIUM SORBATE	0.20			
PURIFIED WATER		PURIFIED WATER	QS 100.00			
CHARACTERISATION AT T0		MACROSCOPIC APPEARANCE	White, smooth, brilliant cream			
		MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. Ø < 7µm			
		pH	6.82			
		VISCOSITY	Needle 6, Rate 50 11520cp			
		CENTRIFUGING	RAS			
Stability monitoring		1 month	2 months	3 months	6 months	
Physical stability	pH AT/40°C		6.60/6.43	6.80/6.34	6.61/6.24	6.54/6.23
	Needle Viscosity 6, rate 50	AT	11080cp	10200cp	11200cp	9680cp
		40°C	11760cp	11400cp	10720cp	9520cp

Chemical stability	Dose compound A Initial %	AT	98.6	100.3	99.7	99.2
		40°C	97	98.1	97.4	95.4

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 18 (0298.0113)

COMPOSITIONS		
Commercial Name	INCI name	%
COMPOUND A	COMPOUND A	0.04
PHENOXETOL	PHENOXYETHANOL	1.00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15.00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2.00
RONACARE ALLANTOIN	ALLANTOIN	0.20
GLYCERINE 4810 VEGETABLE	GLYCERIN	20.00
SIMULGEL 600 PHA	ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	2.5
BENZALKONIUM CHLORIDE	BENZALKONIUM CHLORIDE	0.05
PURIFIED WATER	PURIFIED WATER	5.00
PURIFIED WATER	PURIFIED WATER	QS 100.00
CHARACTERISATION AT T0	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion. $\varnothing < 7\mu\text{m}$
	pH	6.80
	VISCOSITY	Needle 6, Rate 50 10920cp
	CENTRIFUGING	RAS

Stability monitoring			1 month	2 months	3 months	6 months
		pH AT/40°C	6.63/6.37	6.67/6.22	6.62/6.25	6.61/6.28
Physical stability	Viscosity Needle 6, rate 50	AT	13340cp	10450cp	10540cp	10840cp
		40°C	11040cp	NR	10400cp	9240cp
Chemical stability	Dose compound A Initial %	AT	100.2	98.3	99.8	99.4
		40°C	99.9	97.5	99.0	96.8

These results demonstrate good physical and chemical stability of the active ingredient and of the composition as a whole over time.

Formula 19 :

COMPOSITIONS		
Commercial Name	INCI Name	%
COMPOUND A	COMPOUND A	0,01
PHENOXYETOL	PHENOXYETHANOL	1,00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8,00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15,00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2,00
RONACARE ALLANTOIN	ALLANTOIN	0,20
GLYCERINE 4810 VEGETABLE	GLYCERIN	10,00
SIMULGEL 600 PHA	ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	3,00
GLUCONO-DELTA-LACTONE SG	GLUCONOLACTONE	0,25
PROBENZ SP	SODIUM BENZOATE	0,20
PROPYLENE GLYCOL	PROPYLENE GLYCOL	10,00
PURIFIED WATER	PURIFIED WATER	QS 100,00
CHARACTERISATION AT 20	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion.
	pH	5.20
	VISCOSITY	Needle 6, Rate 10 59200cp
	CENTRIFUGING	RAS

Formula 20 :

COMPOSITIONS		
Commercial Name	INCI Name	%
COMPOUND A	COMPOUND A	0.01
PHENOXYETOL	PHENOXYETHANOL	1.00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8.00
ARLAMOI PS15F-IQ	PPG-15 STEARYL ETHER	15.00
ST-CYCLOMETHICONE SNF	CYCLOPENTASILOXANE	2.00
RONACARE ALLANTOIN	ALLANTOIN	0.20
GLYCERINE 4810 VEGETABLE	GLYCERIN	13.00
SIMULGEL 600 PHA	ACRYLAMIDE,AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	3.00
GLUCONO-DELTA-LACTONE SG	GLUCONOLACTONE	0.25
BENZYL ALCOHOL	BENZYL ALCOHOL	1.00
PROBENZ SP	SODIUM BENZOATE	0.20
PROPYLENE GLYCOL	PROPYLENE GLYCOL	7.00
PURIFIED WATER	PURIFIED WATER	QS 100.00
CHARACTERISATION AT TO	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion.
	pH	4.89
	VISCOSITY	Needle 29, Rate 20 29650cp
	CENTRIFUGING	RAS

Formula 21 :

COMPOSITIONS		
Commercial Name	INCI Name	%
COMPOUND A	COMPOUND A	0,01
PHENOXYETOL	PHENOXYETHANOL	1,00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8,00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15,00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2,00
RONACARE ALLANTOIN	ALLANTOIN	0,20
GLYCERINE 4810 VEGETABLE	GLYCERIN	15,00
SIMULGEL 600 PHA	ACRYLAMIDE, AMPS COPOLYMER DISPERSION 10%/ ISOHEXADECANE/ POLYSORBATE 80	3,00
GLUCONO-DELTA-LACTONE SG	GLUCONOLACTONE	0,25
BENZYL ALCOHOL	BENZYL ALCOHOL	1,00
PROBENZ SP	SODIUM BENZOATE	0,20
PROPYLENE GLYCOL	PROPYLENE GLYCOL	5,00
PURIFIED WATER	PURIFIED WATER	QSP 100,00
CHARACTERISATION AT TO	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion.
	pH	4.82
	VISCOSITY	Needle 29, Rate 12 48583cp
	CENTRIFUGING	RAS

Formula 22 :

COMPOSITIONS		
Commercial Name	INCI Name	%
COMPOUND A	COMPOUND A	0,01
PHENOXYETOL	PHENOXYETHANOL	1,00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8,00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15,00
ST-CYCLOMETHICONE SNF	CYCLOPENTASILOXANE	2,00
RONACARE ALLANTOIN	ALLANTOIN	0,20
TITRIPLEX III	EDTA	0,20
GLYCERINE 4810 VEGETABLE	GLYCERIN	20,00
SIMULGEL 600 PHA	ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	2,50
GLUCONO-DELTA-LACTONE SG	GLUCONOLACTONE	0,25
BENZYL ALCOHOL	BENZYL ALCOHOL	1,00
PROBENZ SP	SODIUM BENZOATE	0,20
PURIFIED WATER	PURIFIED WATER	QSP 100,00
CHARACTERISATION AT TO	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion.
	pH	4.97
	VISCOSITY	Needle 29, Rate 20 29500cp
	CENTRIFUGING	RAS

Formula 23 :

COMPOSITIONS		
Commercial Name	INCI Name	%
COMPOUND A	COMPOUND A	0,06
PHENOXYETOL	PHENOXYETHANOL	1,00
MIGLYOL 812N	CAPRYLIC/CAPRIC TRIGLYCERIDES	8,00
ARLAMOL PS15E-LQ	PPG-15 STEARYL ETHER	15,00
ST-CYCLOMETHICONE 5NF	CYCLOPENTASILOXANE	2,00
RONACARE ALLANTOIN	ALLANTOIN	0,20
GLYCERINE 4810 VEGETABLE	GLYCERIN	20,00
SIMULGEL 600 PHA	ACRYLAMIDE, AMPS COPOLYMER DISPERSION 40%/ ISOHEXADECANE/ POLYSORBATE 80	2,50
BENZALKONIUM CHLORIDE	BENZALKONIUM CHLORIDE	0,05
POTASSIUM SORBATE	POTASSIUM SORBATE	0,20
PURIFIED WATER	PURIFIED WATER	QSP 100,00
CHARACTERISATION AT T0	MACROSCOPIC APPEARANCE	White, smooth, brilliant cream
	MICROSCOPIC APPEARANCE	Absence of crystals. Fine, homogeneous emulsion.
	pH	6.64
	VISCOSITY	Needle 5, Rate 10 32320cp
	CENTRIFUGING	RAS
Stability monitoring	1 MONTH	2MONTHS
		3MONTHS
		6MONTHS

Physical stability	pH TA/40°C	6.58/6.41	6.44/6.23	NR	6.48/6.17
	Viscosity AT	309000cp	251000cp	287000cp	300000cp
	pH AT/40°C				
	Rate 1				
Physical stability	Viscosity 40°C	320000cp	374000cp	324000cp	317000cp
	Needle 5				
	Rate 1				

These results demonstrate a good physical stability of the composition as a whole over time.

Example 3: Characterisation of the formulations by cutaneous penetration studies on human skin:

The cutaneous penetration studies enable the formulations to be characterised and the parameters peculiar to each of the formulations to be demonstrated.

Two types of cutaneous penetration studies were carried out ex vivo on human skin. In these studies compound A corresponds to 3''-tert-butyl-4'-(2-hydroxy-ethoxy)-4''-pyrrolidin-1-yl-[1,1';3',1'']-terphenyl-4-carboxylic acid.

The reference gel is described as follows:

Constituents	% by weight
COMPOUND A	0.01
Propylene Glycol	30.00
Ethanol 95-96%	67.99
Klucel HF Pharma	2.00

1- "Single time" cutaneous penetration study:

In this study the formula is applied for 16 hours to the surface of the skin. After the application, compound A (COMPOUND A) is quantified in the different compartments of the skin: stratum corneum, epidermis, dermis and receiving liquid according to a validated bioanalysis method.

The details of the cutaneous application are given in the table below.

Skin: 3 donors, 2 samples per donor

Source	Entire abdominal human skin
Thickness	0.79-1.22mm
Age	39-64 years.
Franz cells	2 cm ²
Volume of receiving liquid	3mL
Barrier function	Evaluated by determination of the Insensitive Loss in Water, acceptable except where contraindicated

Formulations

A: Reference gel containing 100µg/g of COMPOUND A

B: Oil in water emulsion without emulsifier, containing 100µg/g of COMPOUND A (Formula 3)

Application

Application	~2mg/cm ²
Quantity of active ingredient applied	142~241ng/cm ²
Exposure time	16h

Samples taken

Donor compartment lavage	}	"Excess" / Unabsorbed dose	}	Mass balance
Kleenex (enabling the surplus product to be removed)				
1 st strip	}	Total skin	}	Total penetration
Stratum corneum (2-15 strips max)	}			
Epidermis	}			
Dermis	}	Absorbed dose	}	
Receiving Liquid	}			

The bioanalysis was conducted by mass spectrometry in tandem by positive electrospray ionisation using a Xevo device (Waters). The limit of quantification for compound A is 1 ng/mL.

The conditions of LC/MS/MS developed enabled up to 0.1% of the dose applied in each of the compartments to be detected (unabsorbed dose, stratum, epidermis, dermis and receiving liquid).

The technical conditions are given in the table below.

LC column	Hypersil gold 50*2.1mm (UPLC)						
Mobile phase	Phase A : ACN + 0.1% Formic Acid Phase B : H ₂ O + 0.1% Formic acid						
Lavage of Needle	CAN						
Lavage of septum	ACN/H ₂ O 50:50						
Gradient	Time (min)	flow rate	%A	%B	Curve		
	1. Initial	0.700	15.0	85.0	0		
	2. 2.5	0.700	90.0	10.0	6		
	3. 3.20	0.700	90.0	10.0	6		
	4. 3.25	0.700	15.0	85.0	6		
Temperature of columns							
MSMS detection	ESI+ MRM (Positive electrospray)						
	Canal	Reaction	Dwell (secs)	Voltage (cone)	Col. Energy	Tr (min)	Compound
	1: 460.26	> 318.20	0.100	50.0	40.0	1.58	Compound A
							Deuterated internal
	1: 464.06	> 372.10	0.100	55.0	40.0	1.58	standard

Volume Injection	5 μ L
Run time	4 minutes

In this type of “single point” study the parameters considered are:

- a. The distribution profile in the different compartments (qualitative data)
- b. The penetration in the epidermis + dermis compartment (numerical data)

a-Distribution profile in the different compartments:

This profile is shown in Figure 1.

The distribution profile between the different compartments is of the same time for the 2 formulae evaluated: accumulation in the stratum corneum, lower rate of penetration in the epidermis, and very low penetration in the dermis. Compound A is not detected in the receiving liquid.

b-Penetration values in the epidermis + dermis compartment:

The penetration values for the oil in water type emulsion without emulsifier, containing 100 μ g/g (0.01%) of compound A are between 6.8ng/cm² and 10.6ng/cm². The levels of penetration of compound A after application of the oil in water type emulsion without emulsifier tend to be higher than those obtained after application of the reference gel.

2- Penetration kinetics study:

In this type of study the penetration of the active ingredient is quantified in each compartment of the skin after 0.5 h, 1 h, 3 h, 6 h and 24 h of application. The penetration kinetics in each compartment are then determined and characterised.

The details of the cutaneous application are given in the table below:

Skin	3 donors, 2 samples per donor per time, n=6
Source	Abdominal human skin dermatomed from corpse
Thickness	500µm
Age	Not Indicated
Franz cells	1-2cm ²
Volume of Receiving Liquid	Not Indicated
Barrier Function	Evaluated by tritiated water
Products	
Reference gel 100µg/g	Oil in water type emulsion without emulsifier 100µg/g (Formula 1)
Formula Application	~2mg/cm ²
Quantity of active ingredient applied	Between 100-200ng/cm ²
Exposure time	Up to 24h
Samples taken	
Exposure time	0.5, 1, 3, 6, 24h
Lavage of donor compartment	{ } "Excess" / Unabsorbed dose
Kleenex (enabling the surplus product to be removed)	
1 st strip	
Stratum corneum (2-15 strips max)	
Epidermis	
Dermis	
	{ } Total Skin } Mass balance
Analyses	LC/UV and LC/MS
Limit of quantification	1ng/ml

The quantity of active ingredient in each compartment at each time was determined by LC/UV or by LC/MS. The bioanalysis method was validated so that at least 0.1% of the dose applied in each compartment could be detected.

In this type of study the parameters considered are:

- a. The penetration kinetics profile in the epidermis (qualitative data)
- b. The initial rate of penetration in the epidermis
- c. The maximum quantity that has penetrated the epidermis

a. Penetration kinetics profile in the epidermis:

This is shown in Figure 2.

The release kinetics of compound A obtained for the oil in water type emulsion without emulsifier exhibit a high initial gradient followed by a ceiling during which the penetration of compound A no longer increases in the course of time. The reference formula (gel) shows the same kinetics with rapid release for the first few hours, after which a plateau is reached.

As seen in Section 1 ("Single time" cutaneous penetration study), these two formulae have different penetration levels at 16h, and the penetration of compound A in the epidermis after application of the oil in water emulsion without emulsifier tends to be higher than that obtained after application of the reference gel.

b. Initial rate of the kinetics:

The initial value of the rate of the kinetics or gradient in the first 3 hours is $4.2\text{ng/cm}^2/\text{h}$.

c. Maximum quantity in the epidermis:

The maximum quantity in the epidermis is 18.7ng/cm^2 .

Example 4 Tolerance study

In this study:

- 10 subjects received 2 grams of gel (reference gel) applied to 1000 cm² for 4 weeks.

A reference gel is understood to mean a gel described as follows:

Constituents	%
Compound A	0.01
Propylene Glycol	30.00
Ethanol 95-96%	67.99
Klucel HF Pharma	2.00

- 10 subjects received 2 grams of Cream B (oil in water emulsion without emulsifier-Formula 1) applied to 1000 cm² for 4 weeks.

During the study the investigators had the opportunity of changing the area of application where irritation was excessive.

The results of the study are presented in the table below: The numerical values are the number of patients for whom a change of area was made (value N in the table), and the value in brackets is the percentage corresponding to N.

Development of the percentage of subjects for whom there is no change of area of application

		Gel 50µg/g 1000 cm ²	Cream B 50µg/g 1000 cm ²	Gel 50µg/g 2000 cm ²	Gel 100µg/g 1000 cm ²	Gel 25µg/g 1000 cm ²
Day 2	N(%)	-	-	-	-	-
Day 4	N(%)	1 (10)	-	-	-	-
Day 5	N(%)	-	1 (10)	2 (20)	1 (10)	-
Day 6	N(%)	1 (10)	-	-	1 (10)	-
Day 7	N(%)	-	-	2 (20)	1 (10)	1 (10)
Day 8	N(%)	1 (10)	1 (10)	-	2 (20)	1 (10)
Day 9	N(%)	3 (30)	1 (10)	2 (20)	1 (10)	-
Day 10	N(%)	-	-	1 (10)	1 (10)	1 (10)
Day 11	N(%)	2 (20)	1 (10)	-	1 (10)	1 (10)
Day 12	N(%)	-	1 (10)	1 (10)	-	1 (10)
Day 13	N(%)	-	1 (10)	-	-	-
Day 14	N(%)	1 (10)	1 (10)	2 (20)	1 (10)	2 (20)
Day 16	N(%)	1 (10)	1 (10)	-	1 (10)	-
Day 18	N(%)	-	-	-	-	1 (10)
Day 19	N(%)	-	-	-	-	-
Day 24	N(%)	-	1 (10)	-	-	1 (10)
No change in the course of the study	N(%)	-	1 (10)	-	-	1 (10)

Figure 3 shows the percentage of subjects for whom there was no change in the area of application as a function of the day of application.

For example, on day 5, for 90% of the subjects receiving Cream B, there was no need to change the area of application. In other words, 10% of the subjects who received Cream B suffered from an irritation requiring a change of area of application.

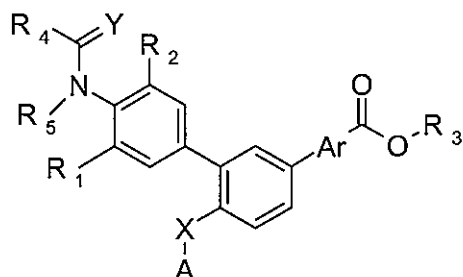
It is therefore established that the irritation occurs more quickly in the subjects who received the gel than in the subjects who received Cream B. A marked difference is observed from day 9 onwards.

CLAIMS

1. An oil-in-water emulsion-type composition comprising

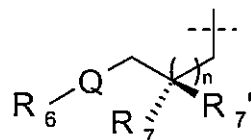
- a fatty phase comprising:

a compound with general formula (I)



where :

- R₁ is a hydrogen atom, an alkyl radical of 1 to 4 carbons or a -CF₃ radical;
- R₂ is a hydrogen atom, an alkyl or alkoxy radical of 1 to 4 carbon atoms or a chlorine atom;
- R₃ is a hydrogen atom, or a linear or branched alkyl or alkoxy radical of 1 to 10 carbon atoms possibly substituted by a methoxy group;
- R₄ is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- R₅ is a hydrogen atom or an alkyl radical of 1 to 3 carbon atoms;
- or R₄ and R₅ together form, with the -N-C(=Y)- bond, a ring of the pyrrolidine, pyrrolidinone, piperidine or piperidinone type;
- Y denotes two hydrogen atoms or a heteroatom such as oxygen or sulfur;
- Ar denotes a 1,4-phenyl, 2,5-pyridyl, 5,2-pyridyl or 2,5-thiophenyl ring;
- X denotes an oxygen atom, possibly substituted by an alkyl or alkylamine chain or a single C-C bond;
- A denotes a hydrogen atom or the following formula:



where

- o Q is an oxygen atom or the bond -NH-;

- R_6 denotes a hydrogen atom, an alkyl radical of 1 to 6 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms, a $-C(O)CH_2$ or $-C(O)CH_2CH_3$ radical;
- R_7 and R_7' denote, independently of each other, a hydrogen atom or a hydroxyl group, on condition that R_7 and R_7' are not simultaneously a hydroxyl group;
- n is equal to 0, 1, 2, 3, 4 or 5 ;

at least one principal solvent of compound (I) and at least one co-solvent oil of compound (I), and

- an aqueous phase comprising at least one gelifying agent.

2. The composition according to Claim 1, characterised in that the compound with general formula (I) is defined so that:

R_1 is a hydrogen atom, the t-butyl or i-propyl radical;

R_2 is a hydrogen atom, the t-butyl or i-propyl radical;

R_3 is a hydrogen atom or the ethyl radical;

R_4 , R_5 are independently from each other the methyl or ethyl radical or together form a pyrrolidine ring;

A is as previously defined, where R_6 denotes a hydrogen atom, the i-propyl or t-butyl radical, a cycloalkyl radical of 3 to 6 carbon atoms, a $-C(O)CH_2$ or $-C(O)CH_2CH_3$ radical.

3. The composition according to Claim 1, characterised in that the compound is 3''-tert-butyl-4'-(2-hydroxy-ethoxy)-4''-pyrrolidin-1-yl-[1,1';3',1'']-terphenyl-4-carboxylic acid.

4. The composition according to any one of the preceding claims, characterised in that it is deprived of an emulsifying agent.

5. The composition according to any one of the preceding claims, characterised in that the gelifying agent is selected from polymers of plant origin, gums, pectins, cellulose and its derivatives, polymers of microbiological origin, such as xanthan gum, and gelifying polymers of synthetic origin, and preferably from:

- the Acrylates/C10-30 Alkyl Acrylate Crosspolymer sold under the name of Pemulen TR-1 or Pemulen TR-2

- the gelifiers in the family of polyacrylamides, such as the mixture Sodium acrylamide/acryloyldimethyltaurate copolymer / isohexadecane / polysorbate 80 sold under the name of Simulgel 600PHA

- the mixture polyacrylamide/isoparaffin C13-14/laureth-7 sold under the name of Sepigel 305,

- the carbomers sold under the name of Ultrez 20®, Ultrez 10®, Carbopol 1382® or Carbopol ETD2020NF®, Carbopol 981 or even Carbopol 980,
- the polysaccharides with, by way of non-exhaustive example, xanthan gum such as Xantural180®, gellan gum sold under the name of Kelcogel, guar gum, cellulose and its derivatives, such as microcrystalline cellulose and carboxymethyl cellulose of sodium sold under the name of Avicel CL-611, hydroxypropylmethylcellulose, in particular the product sold under the name of Methocel E4M premium or hydroxyethylcellulose, in particular the product sold under the name of Natrosol HHX 250®, sodium carboxymethylcellulose, in particular Blanose cellulose gum 7F,
- the family of aluminium magnesium silicates, such as Veegum K,
- the family of acrylic polymers linked to hydrophobic chains such as PEG-150/decyl/SMDI copolymer sold under the name of Aculyn 44,
- the family of modified starches such as modified potato starch, sold under the name of Structure Solanace or their mixtures,
- the family of carrageenans, in particular those distributed among four major families : κ , λ , β , ω such as the Viscarins® and Gelcarins®.

6. The composition according to any one of the preceding claims, characterised in that the principal solvent is selected from among benzyl alcohol, laureth-4, phenoxyethanol, propylene glycol monocaprylate, pentyleneglycol, dimethyl isosorbide and mixtures thereof.

7. The composition according to Claim 6, characterised in that the principal solvent is phenoxyethanol.

8. The composition according to any one of the preceding claims, characterised in that the co-solvent oil is selected from among the caprylic/ capric triglycerides, sweet almond oil, propylene glycol monocaprylate, propylene glycol laurate, sorbitan sesquioleate, diisopropyl adipate, PPG-15 stearyl ester, apricot kernel oil, PEG-6 ester, and mixtures thereof.

9. The composition according to any one of the preceding claims, characterised in that it also contains one or more additives selected from among:

-One or more preserving agents selected from among methyl parabene, propyl parabene, benzalconium chloride, phenoxyethanol sold under the name of phenoxetol, benzyl alcohol sold under the name of benzyl alcohol, Potassium sorbate sold under the name of potassium sorbate, benzoic acid, 2-bromo-2-nitropropane-1,3-diol sold under the name of Bronopol, Chlorohexidine, Chlorohexidine digluconate, chlorocresole and its derivatives, ethyl alcohol and diazolidinyl urea,

-One or more chelating agents such as EDTA (ethylene diamine tetraacetic acid) and its derivatives or salts, dihydroglycerine, citric and tartaric acids, gluconolactone sold under the name of glucono-delta-lactone SG or mixtures thereof,

- One or more antioxidants such as vitamin E and its derivatives, such as DL alpha tocopherol or tocopherol acetate; vitamin C and its derivatives, such as Ascorbyl Palmitate, Butylhydroxy toluene sold under the name of Nipanox BHT,

- One or more palliatives and/or anti-irritants such as PPG-12/SMDI copolymer under the commercial name of Polyolprepolymer-2, glycyrrhetic acid or its derivatives, for example Enoxolone, hyaluronic acid as such or in its form of sodium hyaluronate sold under the commercial name of HYAL. NA PWD PH 15-51-45, allantoin sold under the name of RONACARE ALLANTOINE.

10. The composition according to any one of the preceding claims, characterised in that it also contains a mineral oil.

11. The composition according to any one of the preceding claims, characterised in that it also contains a moistening agent.

12. The composition according to any one of the preceding claims, characterised in that it also contains a silicone oil.

13. The composition according to any one of the preceding claims, characterised in that it also contains ethanol.

14. The composition according to any one of Claims 1 to 13, characterised in that it comprises the following ingredients:

from 0.00001% to 1% by weight and preferably from 0.0001 to 0.1 % by weight and more preferably from 0.001 by weight to 0.1% of compound of formula (I)

from 0.005 to 10 % by weight and preferably from 1 to 5% by weight of gelifying agent

from 0.2 to 5% by weight and preferably from 0.5 to 2% by weight of principal solvent

from 0.5 to 50% by weight and preferably from 4 to 30% by weight of co-solvent oil(s), and optionally:

from 0 to 20% by weight and preferably from 0 to 5% by weight of mineral oil(s)

from 0 to 50% by weight and preferably from 5 to 35% by weight of polyol(s)

from 0 to 10% by weight and preferably 0 to 4% by weight of silicone oil(s)

from 0 to 5% by weight and preferably from 0.01 to 2% by weight of preservative agent(s)

from 0 to 30% by weight and preferably from 0 to 10% by weight of ethanol

from 0 to 15% by weight and preferably from 0.1 to 10% by weight of additive(s).

15. The composition according to any one of the preceding claims, characterised in that the maximum quantity of active ingredient absorbed in the dermis and epidermis 16 hours after application is between 6 ng/cm² and 19 ng/cm².

16. The composition according to Claim 15, characterised in that the maximum quantity of active ingredient absorbed in the dermis and epidermis 16 hours after application is between 6.8 ng/cm² and 10.6 ng/cm².

17. The composition according to any one of the preceding claims, characterised in that the maximum quantity of active ingredient absorbed in the epidermis is obtained between 3 and 10 hours after application.

18. The composition according to any one of Claims 1 to 17 for use as a medicinal product.

19. The composition according to any one of Claims 1 to 18 for use for the treatment of one or more of the following pathologies:

-Dermatological complaints associated with a keratinisation disorder relating to cellular differentiation and proliferation, particularly for treating common acne, comedonic acne, polymorphic acne, rosacea acne, nodulocystic acne, conglobata acne, senile acne and secondary acnes such as solar, medicamentous or professional acne;

-Keratinisation disorders, in particular ichthyoses, ichthyosiform conditions, lamellar ichthyosis, Darrier's disease, palmoplantar keratodermias, leukoplasias, pityriasis rubra pilaris and leukoplasiform conditions, cutaneous or mucous (oral) lichen;

-Dermatological disorders with an inflammatory immune-allergic component, with or without cellular proliferation disorder, and in particular all forms of psoriasis, whether cutaneous, mucous or ungueal, and even psoriatic rheumatism, or atopic dermatitis and the different forms of eczema;

-Cutaneous disorders due to exposure to UV radiation, as well as to repair or control ageing of the skin, whether photo-induced or chronological, or to reduce pigmentations and actinic keratoses, or all pathologies associated with chronological or actinic ageing, such as xerosis, pigmentations and wrinkles;

-Any condition associated with benign dermal or epidermal proliferations, whether or not of viral origin, such as common warts, flat warts, molluscum contagiosum and verruciform epidermodysplasia, oral or florid papillomatoses;

-Dermatological complaints such as immune dermatoses such as erythematous lupus, bullous immune diseases and collagenic diseases such as sclerodermia;

-Stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy;

-Healing complaints, or to prevent or repair stretch marks, or even to promote healing;

-Any disorder of fungal origin in the cutaneous region, such as tinea pedis and tinea versicolor;

-Pigmentation disorders such as hyperpigmentation, melasma, hypopigmentation or vitiligo ;

-Cancerous or pre-cancerous, cutaneous or mucous conditions such as actinic keratoses, Bowen's disease, carcinomas in-situ, keratoacanthoma and skin cancers such as basocellular carcinoma (BCC), spinocellular carcinoma (SCC) and cutaneous lymphomas such as T lymphoma.