



(51) International Patent Classification:

A61Q 19/08 (2006.01) A61K 8/34 (2006.01)

A61K 8/11 (2006.01) A61K 8/49 (2006.01)

A61K 8/14 (2006.01) A61K 8/67 (2006.01)

(21) International Application Number:

PCT/EP2020/062369

(22) International Filing Date:

05 May 2020 (05.05.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1906362.7 06 May 2019 (06.05.2019) GB

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: COSMETIC INGREDIENT COMPRISING RETINOL IN MULTILAYER CRYSTALLINE MICROCAPSULES

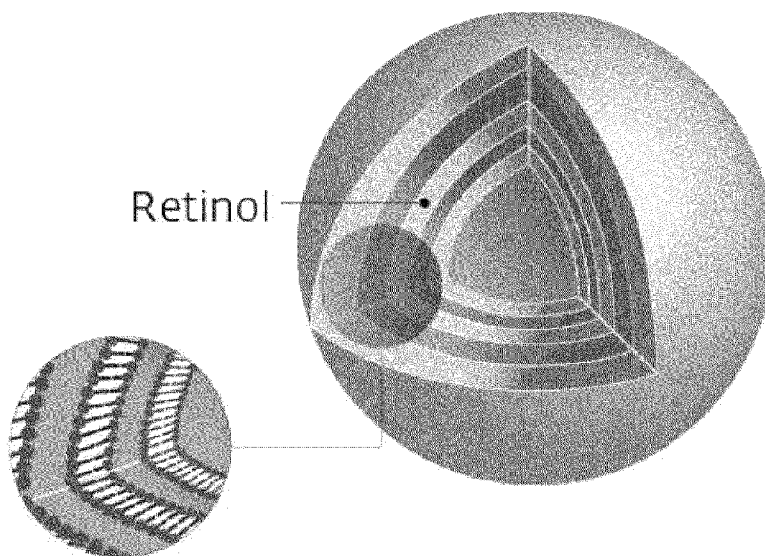


Figure 1

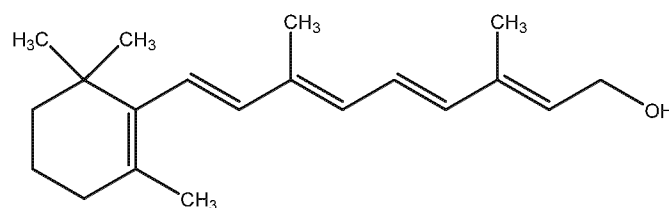
(57) Abstract: A cosmetic ingredient comprising retinol is provided, which displays improved stability and reduced skin irritation. Furthermore, cosmetic compositions comprising the same and methods of use thereof are described.



COSMETIC INGREDIENT COMPRISING RETINOL IN MULTILAYER CRYSTALLINE MICROCAPSULES

The invention relates to a cosmetic ingredient comprising retinol displaying improved stability and reduced skin irritation, to cosmetic compositions comprising the same, and to methods of use thereof.

- 5 Retinol, also known by its common name of vitamin A, is a fat-soluble vitamin composed of a cyclohexene ring with a side chain containing conjugated polyunsaturation. Retinol has the following structure:



- 10 The retinoid family comprises vitamin A (retinol) and its natural derivatives such as retinal (retinaldehyde), retinoic acid, and retinyl esters, as well as a large number of synthetic derivatives.

Retinol has long been recognized in the pharmaceutical, nutritional, and cosmetic industry, as an active substance of great benefit. Retinol is essential to many body or biological functions and it plays an important role particularly for vision.

- 15 Because of its important physiological function, especially in the regulation of proliferation and differentiation of a number of cell types, retinol is an extremely valuable substance. In the cosmetics industry there is great interest in the increased use of retinol, particularly in dermatological formulations. Retinol containing vitamin preparations are being marketed by the food industry. Retinol has also been used in pharmaceutical formulations.
- 20 Topical application of retinol stabilizes the vitamin A balance in the skin, which balance can be permanently impaired in particular by exposure to UV light. The deficiency of vitamin A leads to damage, particularly of the epidermis, and to increased formation of wrinkles ("photo-aging"). Deficiency of vitamin A also leads to a loss of the skin's elasticity and weakens the barrier function of the skin against microorganisms.
- 25 Retinol has conventionally been used in the treatment of acne, as well as repair of skin damage caused either by age or by over-exposure to the sun. The effects of retinol on cell differentiation

make it possible to envisage its use for effectively combating the appearance of wrinkles and fine lines, and for combating dryness, roughness and/or stiffness of the skin. In addition, retinol is active as antioxidant in the regeneration of tissues. Repeated application of cosmetic compositions containing retinol has enabled wrinkles to be removed, the skin to be rendered
5 smooth and small cracks in the epidermis to be repaired.

In particular, retinol is a gold standard when it comes to reversing the signs of skin ageing. It is known to influence a variety of cellular processes, such as cellular growth and differentiation, cell surface alterations, and immune modulation. Retinol inhibits UV induction of MMP (matrix metalloproteinase) in photo-aged skin, stimulates collagen synthesis and significantly improves
10 fine wrinkles. Applied topically, retinol has the power to boost collagen production, increase cell turnover and accelerate skin renewal for firmer, smoother and more evenly-toned skin. This results in reduction of fine lines and wrinkles, fading of age spots, prevention of cell damage and premature skin ageing.

However, being a highly reactive molecule, retinol is one of the trickiest ingredients to work with.
15 Its stability can be compromised by such factors as solvent, temperature, oxygen and light.

The main problem that prevents the wide spread use of retinol is its sensitivity to oxidation, in particular oxidation caused by exposure to light. An autoxidation reaction takes place at the side chain of the molecule which contains the conjugated unsaturation. This reaction leads to the formation of numerous decomposition products, to isomerizations and to polymerizations. The
20 originally crystalline retinol material becomes a viscous mass; and the pale yellow color of pure retinol becomes noticeably darker. As a result of peroxides which are formed as intermediates, the potentially toxic results of these formulations increases. Also, cosmetically desired results of the remaining intact retinol are reduced.

Instead of using the uncombined free retinol, which is very sensitive to oxidation, cosmetics,
25 especially anti-wrinkle creams, often contain the less active, but more stable retinyl esters. Examples of these more stable retinyl esters particularly include retinyl acetate and retinyl palmitate.

Long chain retinyl esters, especially retinyl palmitate, have been used extensively in skin cosmetic compositions. However, it has been found that retinol or short chain esters of retinol
30 are more efficacious than long chain esters of retinol: It is believed that retinyl palmitate does not hydrolyze *in vivo* to produce retinol and/or does not penetrate skin. Retinol and short chain retinyl

esters, on the other hand, are less stable and, specifically, rapidly degrade in the presence of water.

For these reasons, among others, scientists working in the field have had difficulty in formulating cosmetic, dermatological, and pharmaceutical compositions of stable retinol, which would be useful for cosmetic or dermatological needs. Nevertheless, because of the many beneficial effects attributed to retinol, numerous attempts have been made to overcome these difficulties.

WO 03/105806 A1 provides an overview on the various means proposed for stabilizing retinol in cosmetic compositions. They include the reversal of the phases to form water-in-oil emulsions, the addition of stabilizers such as antioxidants, UV-absorbers, or chelating agents, the formation of stabilizing complexes, the use of retinyl esters, encapsulation, or physical entrapment. For each of these attempts, WO 03/105806 A1 also describes their specific drawbacks.

In conclusion, none of the technologies disclosed in the prior art allows for satisfactorily stabilizing retinols over an extended period of time.

It is therefore still desirable to provide an effective process for stabilizing retinol to provide cosmetic, dermatological and pharmaceutical compositions, which are stable enough at effective retinol levels, to guarantee the results desired in storing and handling these compositions, and enable a gradual and prolonged release of retinol, which have little or no irritancy and which do not necessitate special ingredients or manufacturing, storage and handling precautions.

The present invention provides retinol in the form of multilayer crystalline microcapsules.

Thus, the present invention relates to a cosmetic ingredient comprising multilayer crystalline microcapsules comprising retinol, or in other words, to retinol-containing multilayer crystalline microcapsules. These terms are used interchangeably throughout this application.

It has been found that by incorporating the retinol in multilayer crystalline microcapsules, it is possible to significantly improve its long term stability, to enhance skin penetration, and to reduce skin irritation.

Figure 1 shows a schematic visualization of such a multilayer crystalline microcapsule. Within the microcapsule, several hydrophilic and lipophilic layers alternate. Retinol is mostly contained in the lipophilic layers.

In a preferred embodiment, the multilayer crystalline microcapsules are non-ionic. This means that they comprise non-ionic surfactants as a liquid crystal forming material. Alternatively, it would also be possible that the multilayer crystalline microcapsules are cationic.

It has been found that non-ionic multilayer crystalline microcapsules enable better penetration into the skin, where retinol is slowly released. This provides not only a more efficient delivery of retinol to the lower skin layers, in particular the *Stratum Corneum*, but also prevents any adverse reactions, such as skin irritation.

In an embodiment, the multilayer crystalline microcapsules comprise 15 to 75 wt% of non-ionic surfactants. Preferably, the multilayer crystalline microcapsules comprise 15 to 50 wt% of non-ionic surfactants, even more preferably 15 to 30 wt%, and most preferably about 20 wt%. These ranges have been found to provide optimal stability and viscosity of the multilayer crystalline microcapsules, thus facilitating the handling and manufacturing.

Suitable non-ionic surfactants include, but are not limited to, fatty alcohols, polysorbates, glycerol esters of fatty acids, sucrose esters, and mixtures thereof.

Fatty alcohols (or long-chain alcohols) are usually high-molecular-weight, straight-chain primary alcohols, but can also range from as few as 4–6 carbons to as many as 22–26, derived from natural fats and oils. The precise chain length varies with the source. Some commercially important fatty alcohols are lauryl, stearyl, and oleyl alcohols. They are usually colorless oily liquids (for smaller carbon numbers) or waxy solids. Fatty alcohols are mainly used in the production of detergents and surfactants. They are components also of cosmetics, foods, and industrial solvents. Due to their amphipathic nature, fatty alcohols behave as nonionic surfactants. They find use as co-emulsifiers, emollients and thickeners in cosmetics and food industry. About 50% of fatty alcohols used commercially are of natural origin, the remainder being synthetic.

Cetostearyl alcohol has been found to be particularly useful in the present invention. Cetostearyl alcohol (also called cetearyl alcohol or cetylstearyl alcohol) is a mixture of fatty alcohols, consisting predominantly of cetyl and stearyl alcohols and is classified as a fatty alcohol. It is used as an emulsion stabilizer, opacifying agent, and foam boosting surfactant, as well as an aqueous and non-aqueous viscosity-increasing agent. It imparts an emollient feel to the skin and can be used in water-in-oil emulsions, oil-in-water emulsions, and anhydrous formulations. It is commonly used in hair conditioners and other hair products.

Docosan-1-ol (also known as behenyl alcohol) has also been found to be particularly useful in the present invention. Docosan-1-ol is a saturated fatty alcohol used traditionally as an emollient, emulsifier, and thickener in cosmetics.

Polysorbates are oily liquids derived from ethoxylated sorbitan (a derivative of sorbitol) esterified with fatty acids. Polysorbates are a class of emulsifiers commonly used in cosmetic, pharmaceutical and food preparations. Typical examples are polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), and polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). Polysorbate 60 has been found to be particularly useful in the present invention.

Fatty acid esters (FAEs) are a type of ester that result from the combination of a fatty acid with an alcohol. When the alcohol component is glycerol, the fatty acid esters produced can be monoglycerides, diglycerides, or triglycerides. Glycerol esters of fatty acids occur as colorless to brown powders, flakes, coarse powders, or granular or waxy lumps, or are colorless to brown semi-fluids or liquids.

Glyceryl linoleate has been found to be particularly useful in the present invention.

Sorbitan monostearate has also been found to be particularly useful in the present invention. Sorbitan monostearate is an ester of sorbitan (a sorbitol derivative) and stearic acid and is sometimes referred to as a synthetic wax. Sorbitan monostearate is primarily used as an emulsifier to keep water and oils mixed. Typical applications include food and healthcare products, as well as cosmetic compositions.

In an embodiment of the present invention, the non-ionic surfactants are selected from the group consisting of cetostearyl alcohol, a polysorbate, glyceryl linoleate, docosan-1-ol, sorbitan monostearate, and mixtures thereof.

The non-ionic surfactants may be used separately, mixed directly prior to use, or used in the form of commercial products comprising a mixture of two or more such non-ionic surfactants. Commercially available products include, but are not limited to, SP Polawax NF MBAL-PA-(RB) from Croda (mixture of cetostearyl alcohol and polysorbate 60 in a ratio of approximately 4:1), Lanette O from BASF (cetostearyl alcohol), Tween 60 from Croda (polysorbate 60), Dimodan from Danisco (glyceryl linoleate), Lanette 22 from BASF (docosan-1-ol), and Dehymuls SMS from BASF (sorbitan monostearate).

A mixture of cetostearyl alcohol and polysorbate 60 has been found to provide particularly good results in the cosmetic ingredient of the present invention. The two surfactants have been combined and tested in various ratios. Preferred ratios range from 4:1 to 1:1.

Depending on temperature, agitation speed, surfactants, ratio of surfactants, time, and cooling rate, the average diameter of the multilayer crystalline microcapsules may vary. Preferably, the multilayer crystalline microcapsules have an average diameter of 0.3 to 100 μm , more preferably of 1 to 50 μm , and most preferably of 2 to 30 μm .

The multilayer crystalline microcapsules of the present invention may comprise retinol in any suitable concentration. In particular, the multilayer crystalline microcapsules may comprise 1 to 15 wt% of retinol, more preferably 5 to 12 wt% of retinol, and most preferably about 10 wt% of retinol.

Retinol may be incorporated in the multilayer crystalline microcapsules in pure form or in combination with other active ingredients, stabilizers and/or excipients. For instance, retinol may be included as a 1:1 mixture of retinol and polysorbate 20, which is commercially available from BASF under the name "Retinol 50C".

Alternatively or in addition to retinol, the multilayer crystalline microcapsules of the present invention may also comprise one or more cosmetically acceptable retinol derivatives, such as retinyl palmitate and/or retinyl propionate.

Typically, the hydrophilic layers of the multilayer crystalline microcapsules of the present invention are formed by a polar solvent.

Therefore, in one embodiment of the invention, the cosmetic ingredient further comprises a polar solvent. Preferred polar solvents include, but are not limited to, water, glycerine, 1,3-propanediol, and mixtures thereof, in particular water. Typically, the multilayer crystalline microcapsules comprise about 10 to 90 wt% of the polar solvent, more preferably about 30 to 70 wt% of the polar solvent, and most preferably about 40 to 60 wt% of the polar solvent, for instance about 50 wt%.

In order to even further improve the stability, the cosmetic ingredient of the present invention may further comprise an antioxidant. Preferred antioxidants include, but are not limited to, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and mixtures thereof. The antioxidant may be comprised in any suitable concentration, for instance at about 2 wt%.

In a preferred embodiment, the cosmetic ingredient of the present invention comprises the multilayer crystalline microcapsules comprising a mixture of cetostearyl alcohol and polysorbate 60 as non-ionic surfactants, a mixture of retinol and polysorbate 20, butylated hydroxytoluene and butylated hydroxyanisole as antioxidants, and water as polar solvent. Preferably, these ingredients are contained in the preferred concentrations described above.

A particularly preferred embodiment is described in example 4.

The cosmetic ingredient of the present invention may be used in pure form or in combination with other active ingredients and/or excipients. In particular, it may optionally further contain other cosmetic active ingredients. Any cosmetic active ingredients commonly used in the preparation of cosmetic preparations for use on the human skin may be employed in the present invention.

The cosmetic ingredient of the present invention may optionally further contain solvents, excipients, and/or other adjuvants. Any solvents, excipients, and/or other adjuvants commonly used in the preparation of cosmetic preparations for use on the human skin may be employed in the present invention.

For instance, the cosmetic ingredient of the present invention may further comprise one or more preservatives, such as, for instance, phenoxyethanol and/or ethylhexylglycerin.

The cosmetic ingredient of the present invention is dispersible in water.

The cosmetic ingredient of the present invention is particularly suitable for skin care applications, especially for anti-aging products.

The cosmetic ingredient of the present invention is advantageously used in cosmetic compositions, in particular in skin care compositions. It can be added at the end of the formulation process, below 40 °C under gentle stirring, at a pH between 4 and 8.

Therefore, in a further aspect, the present invention provides a cosmetic composition, and in particular a skin care composition, comprising the above described cosmetic ingredient and a cosmetically acceptable excipient.

More particularly, the present invention provides an anti-aging skin care composition.

It has been found that by applying the cosmetic ingredient of the present invention or the cosmetic composition of the present invention to the skin, it is possible to significantly reduce wrinkles and improve skin texture. It provides anti-wrinkle, skin lifting, anti-age spots, and anti-acne activity and works as a collagen booster.

5 Particular uses of the cosmetic active agent of the present invention include, but are not limited to, anti-ageing serums or creams, anti-ageing products for the reduction of deep wrinkles, intensive treatments for facial rejuvenation, nasolabial anti-wrinkles products, anti-crow's feet products, anti-age spots serums, skin care for mature skin.

Thus, the present invention provides a cosmetic composition comprising the cosmetic ingredient
10 of the present invention, in particular in the preferred embodiments outlined herein.

Nowadays, many countries have legal/regulatory requirements restricting the maximum concentration of retinol in cosmetic products to 0.3 wt%. This is mainly due to the known side effects of retinol, such as skin irritation. Thus, depending on the concentration of retinol in the cosmetic ingredient of the present invention, the latter's concentration in a cosmetic composition
15 may have to be adapted accordingly.

Typically, the cosmetic ingredient of the present invention will be used in a concentration of about 0.1 to 3.0 wt% in the cosmetic composition, more preferably in a concentration of about 1.0 to 2.5 wt%, for instance in a concentration of about 2 wt%.

However, since the cosmetic ingredient of the present invention has been found to avoid skin
20 irritation (see example 9 below), it is also conceivable to include higher concentrations of the retinol-containing multilayer crystalline microcapsules in a cosmetic composition.

Cosmetic compositions, and in particular skin care compositions, of the present invention may contain one or more cosmetically acceptable excipients. Any excipients commonly used in the preparation of cosmetic preparations for use on the human skin may be employed in the present
25 invention. Suitable excipients include, but are not limited to ingredients that can influence organoleptic properties, penetration of the skin, and the bioavailability of the cosmetic active agent of the present invention. More specifically, they include liquids, such as water, oils or surfactants, including those of petroleum, animal, plant or synthetic origin, such as and not restricted to, peanut oil, soybean oil, mineral oil, sesame oil, castor oil, polysorbates, sorbitan
30 esters, ether sulfates, sulfates, betaines, glycosides, maltosides, fatty alcohols, nonoxynols, poloxamers, polyoxyethylenes, polyethylene glycols, dextrose, glycerol, and the like.

The formulation for topical application to the skin may take any physical form. For instance, the cosmetic composition, and in particular the skin care composition, may be in the form of a liposome composition, mixed liposomes, oleosomes, niosomes, ethosomes, milliparticles, microparticles, nanoparticles and solid-lipid nanoparticles, vesicles, micelles, mixed micelles of surfactants, surfactant-phospholipid mixed micelles, millispheres, microspheres and nanospheres, lipospheres, millicapsules, microcapsules and nanocapsules, as well as microemulsions and nanoemulsions, which can be added to achieve a greater penetration of the cosmetic active agent of the present invention.

The cosmetic composition, and in particular the skin care composition, may be produced in any solid, liquid, or semi-solid form useful for application to the skin topically or by transdermal application. Thus, these preparations of topical or transdermal application include, but are not restricted to, creams, multiple emulsions, such as and not restricted to, oil and/or silicone in water emulsions, water-in-oil and/or silicone emulsions, water/oil/water or water/silicone/water type emulsions, and oil/water/oil or silicone/water/silicone type emulsions, micro-emulsions, emulsions and/or solutions, liquid crystals, anhydrous compositions, aqueous dispersions, oils, milks, balsams, foams, aqueous or oily lotions, aqueous or oily gels, cream, hydro-alcoholic solutions, hydro-glycolic solutions, hydrogels, liniments, sera, soaps, face masks, serums, polysaccharide films, ointments, mousses, pomades, pastes, powders, bars, pencils and sprays or aerosols (sprays), including leave-on and rinse-off formulations.

In order to achieve the beneficial effects described herein, the cosmetic ingredient or cosmetic composition of the present invention are advantageously applied to the skin, in particular to facial skin.

Throughout this application, the term "skin" refers in particular to human skin.

The present invention thus also provides a method of reducing the signs of aging in skin, comprising the step of applying the cosmetic ingredient or the cosmetic composition of the present invention to the skin. In particular, the method comprises the application to facial skin.

The effects of the cosmetic ingredient and cosmetic composition of the present invention are particularly advantageous for skin areas that are visible and exposed, and that commonly display signs of aging, such as wrinkles or age spots. These include, but are not limited to, the face, neck, neckline, hands and forearms.

The present invention also relates to the use of the cosmetic ingredient or the cosmetic composition of the present invention for reducing the signs of aging in skin.

This use includes, in particular, the reduction of wrinkles.

In a further aspect, the present invention provides a method of reducing the signs of aging in skin, comprising the step of applying the cosmetic ingredient of the present invention or the cosmetic composition of the present invention to the skin, in particular to facial skin.

As has been mentioned above, two of the main advantageous of the cosmetic ingredient of the present invention are the improvement of retinol stability and the reduction of skin irritation.

Therefore, in a further aspect, the present invention relates to a method of stabilizing retinol, comprising the step of preparing multilayer crystalline microcapsules comprising retinol.

In another aspect, the present invention relates to a method of reducing skin irritation of retinol, comprising the step of preparing multilayer crystalline microcapsules comprising retinol.

In the above two methods, the possible and preferred embodiments described above for the retinol-containing multilayer crystalline microcapsules of the present invention also apply.

The present invention is further illustrated by means of the following non-limiting examples:

Example 1: Preparation of Retinol-Containing Multilayer Crystalline Microcapsules Based on a 4:1 Mixture of Cetostearyl Alcohol and Polysorbate 60

The following ingredients were used in the preparation:

Trade name	INCI name	Supplier	Amount [g]	Concentration [wt%]
SP Polawax NF MBAL-PA-(RB)	>75% Cetostearyl alcohol / 0-25% Polysorbate 60*	Croda	300	20
Retinol 50C	1:1 Retinol / Polysorbate 20	BASF	300	20
BHT	Butylated hydroxytoluene	Brenntag	30	2
Water		--	855	57
Euxyl 9010	90:10 Phenoxyethanol / Ethylhexylglycerin	Schülke	15	1

* Testing of several batches showed an approximate ratio of 4:1

Process:

SP Polawax NF MBAL-PA-(RB) and BHT were placed in a reaction vessel (316L stainless steel, 6 liters) at room temperature and then heated to 65 °C while mixing. The reaction vessel was evacuated and flooded with Argon. Retinol 50C was added at 65°C and the resulting mixture was stirred under argon at 65 °C for about 15 min until it became homogenous, as confirmed visually.

Euxyl 9010 was dissolved under stirring in water and the solution was heated to 40-50 °C and then added to the above retinol-containing mixture. The reaction vessel was again evacuated and flooded with Argon. The resulting mixture was stirred and homogenized at 65 °C for 30 min, and then cooled down to 35 °C over 90 min while stirring slowly.

The retinol-containing multilayer crystalline microcapsules thus obtained had a pasty appearance and a light yellow color. They were stored in the fridge at 4-8 °C until further use.

Example 2: Preparation of Retinol-Containing Multilayer Crystalline Microcapsules Based on a 4:1 Mixture of Cetostearyl Alcohol and Polysorbate 60, Industrial Scale

The following ingredients were used in the preparation:

Trade name	INCI name	Supplier	Amount [g]	Concentration [wt%]
SP Polawax NF MBAL-PA-(RB)	>75% Cetostearyl alcohol / 0-25% Polysorbate 60*	Croda	4'000	20
Retinol 50C	1:1 Retinol / Polysorbate 20	BASF	4'400	22
BHT	Butylated hydroxytoluene	Brenntag	400	2
Water		--	11'000	55
Euxyl 9010	90:10 Phenoxyethanol / Ethylhexylglycerin	Schülke	200	1

* Testing of several batches showed an approximate ratio of 4:1

Process:

SP Polawax NF MBAL-PA-(RB) and BHT were placed in a reaction vessel (316 L stainless steel, 40 L) at room temperature and then heated to 55 °C while mixing. The reaction vessel was evacuated and flooded with Argon. Retinol 50C was added at 55 °C and the resulting mixture was stirred under argon at 55 °C for about 15 min until it became homogenous, as confirmed visually.

Euxyl 9010 was dissolved under stirring in water and the solution was heated to 53-56 °C and then added to the above retinol-containing mixture. The reaction vessel was again evacuated and flooded with Argon. The resulting mixture was stirred and homogenized at 55 °C for 30 min, and then cooled down to 30-35 °C over 90 min while stirring slowly.

- 5 The retinol-containing multilayer crystalline microcapsules thus obtained had a pasty appearance and a light yellow color. They were stored in the fridge at 4-8 °C until further use.

Figures 2 and 3 show microscopic photographs of the retinol-containing multilayer crystalline microcapsules, as obtained in example 2, in 10-fold (Figure 2) and 20-fold (Figure 3) magnification, respectively. One drop of the retinol-containing multilayer crystalline microcapsules was directly applied to a slide and covered with a borosilicate cover glass. The photographs were taking using polarized light with crossed polars. Figure 3 shows an extract of Figure 1.

Each of the spherical particles found in these photographs corresponds to one retinol-containing multilayer crystalline microcapsule. A birefringence is observed, confirming the crystallinity. In addition, the appearance of a Malteze cross is typical for the multilayer crystalline microcapsules.

Example 3: Preparation of Retinol-Containing Multilayer Crystalline Microcapsules Based on a 1:1 Mixture of Cetostearyl Alcohol and Polysorbate 60

The following ingredients were used in the preparation:

Trade name	INCI name	Supplier	Amount [g]	Concentration [wt%]
Lanette O	Cetostearyl alcohol	BASF	60	15
Tween 60	Polysorbate 60	CRODA	60	15
Retinol 50C	1:1 Retinol / Polysorbate 20	BASF	72	18
BHT	Butylated hydroxytoluene	Brenntag	8	2
Water		--	196	49
Euxyl 9010	Phenoxyethanol / Ethylhexylglycerin	Schülke	4	1

20 Process:

Lanette O, Tween 60, and BHT were placed in a reaction vessel (316L stainless steel, 2 liters) at room temperature and then heated to 65 °C while mixing. Retinol 50C was added at 65 °C and the resulting mixture was stirred at 65 °C for about 15 min until it became homogenous, as confirmed visually.

- 5 Euxyl 9010 was dissolved under stirring in water and the solution was heated to 40-50 °C and then added to the above retinol-containing mixture. The resulting mixture was stirred and homogenized at 65 °C for 30 min, and then cooled down to 35 °C over 90 min while stirring slowly.

10 The retinol-containing multilayer crystalline microcapsules thus obtained had a pasty appearance and a light yellow color. They were stored in the fridge at 4-8 °C until further use.

Example 4: Skin Care Composition Comprising Retinol-Containing Multilayer Crystalline Microcapsules

Using the retinol-containing multilayer crystalline microcapsules from example 1, the following skin care composition was prepared:

INCI name	Trade name	Supplier	Concentration [wt%]
AQUA/WATER		--	87.7
CETYL ALCOHOL (25-50 wt%), GLYCERYL STEARATE (25-50 wt%), PEG-75 STEARATE (10-24.9 wt%), CETETH-20 (5-9.9 wt%), STEARETH-20 (5-9.9 wt%)	Emulium Delta	Gattefossé	5.0
ISODECYL NEOPENTANOATE	Dub VCI	Stéarinerie Dubois	4.5
Retinol-containing multilayer crystalline microcapsules from example 1		--	2.0
PHENOXYETHANOL, METHYL PARABEN, PROPYL PARABEN, ETHYL PARABEN	Phenonip XB	Clariant	0.4
DIMETHICONE	Xiameter pmx-200 silicone fluid 350cSt	Dow Corning	0.3
FRAGRANCE	--	Givaudan	0.1

Thus, the resulting cosmetic composition had a retinol concentration of 0.2%.

Example 5: Skin Care Composition Comprising Free Retinol (Comparative Example)

For comparison, the following skin care composition was prepared:

INCI name	Trade name	Supplier	Concentration [wt%]
AQUA/WATER		--	89.3
CETYL ALCOHOL, GLYCERYL STEARATE, PEG-75 STEARATE, CETETH-20, STEARETH-20	Emulium Delta	Gattefossé	5.0
ISODECYL NEOPENTANOATE	Dub VCI	Stéarinerie Dubois	4.5
RETINOL, POLYSORBATE 20	Retinol 50C	BASF	0.4
PHENOXYETHANOL, METHYL PARABEN, PROPYL PARABEN, ETHYL PARABEN	Phenonip XB	Clariant	0.4
DIMETHICONE	Xiameter pmx-200 silicone fluid 350cSt	Dow Corning	0.3
FRAGRANCE	--	Givaudan	0.1

Thus, the resulting cosmetic composition had a retinol concentration of 0.2%.

5 Example 6: Placebo Skin Care Composition (Comparative Example)

For comparison, the following placebo skin care composition without retinol was prepared:

INCI name	Trade name	Supplier	Concentration [wt%]
AQUA/WATER		--	89.7
CETYL ALCOHOL, GLYCERYL STEARATE, PEG-75 STEARATE, CETETH-20, STEARETH-20	Emulium Delta	Gattefossé	5.0
ISODECYL NEOPENTANOATE	Dub VCI	Stéarinerie Dubois	4.5
PHENOXYETHANOL, METHYL PARABEN, PROPYL PARABEN, ETHYL	Phenonip XB	Clariant	0.4

PARABEN			
DIMETHICONE	Xiameter pmx-200 silicone fluid 350cSt	Dow Corning	0.3
FRAGRANCE	--	Givaudan	0.1

Example 7: Stability Testing

The stability of the following three different samples containing retinol was tested in a gel:

A. Retinol-containing multilayer crystalline microcapsules from example 1

B. KemSpheres, a commercially available product from Clariant containing 8% retinol in encapsulated form (INCI: Water (aqua), Caprylic/Capric Triglyceride, Glycerin, Retinol, Polysorbate 20, Cetyl Palmitate, Phenoxyethanol, Triethanolamine, Ceramide 3)

C. Retinol 50C ("free retinol")

The retinol samples A, B, and C, respectively, were added to the below gel in an amount such that the resulting gel contained 0.3 wt% of retinol.

INCI name	Trade name	Supplier	Concentration [wt%]
Carbomer	Carbopol 940	Lubrizol	0.6
Sodium Hydroxide		Merck	0.3
Glycerin	Glycerine 99.5% (FG, PG)	Thommen-Furler	5.0
Phenoxyethanol / Ethylhexylglycerin	Euxyl PE 9010	Schülke	1.0
Retinol sample A, B or C			
Water			Qsp.

The gel samples were placed in HDPE bottles and maintained at three different temperature conditions: refrigeration (4-8 °C), room temperature (air-conditioned laboratory, 24±3 °C) and oven (45 °C).

The retinol content was confirmed by Liquid Chromatography with photometric detection (HPLC-DAD).

After 150 days of storage, the retinol content was measured:

- Sample A still contained 67% of the original retinol content
- Sample B still contained 33% of the original retinol content
- No retinol was detected for sample C.

5 Thus, the multilayer crystalline microcapsules of the present invention allow for significantly improving the stability of retinol, compared to both free retinol and commercially available encapsulated retinol.

Example 8: Skin Penetration (ex vivo Study)

Tested samples

10 The skin penetration of the following two materials was tested:

D. Retinol 50C (free retinol) at a concentration of 0.3%

E. Retinol-containing multilayer crystalline microcapsules from example 1 at a concentration of 1.5%

15 Thus, both samples contained pure retinol at a concentration of 0.15%. The two samples were prepared immediately before the incubation with the skin explants described below.

Experiment 1: skin penetration after 8 hours

Explants of frozen abdominal skin from a female, 37-year old donor were topically incubated with sample D or E for 8 hours at 32 °C. After this 8-hour incubation phase, the skin surface was
20 cleaned to eliminate any excess of the product and skin explants were frozen at -80 °C.

Experiment 2: skin penetration after 7 days

Fresh breast skin explants from a female, 18-year old donor were topically incubated with sample D or E for 7 days with daily topical application. The skin explants were maintained in survival in a culture system with culture medium renewal every two days for 7 days and
25 incubated at 37 °C in humid atmosphere. After this 7-day incubation phase, the skin surface was cleaned to eliminate any excess of the product and skin explants were frozen at -80 °C.

Raman micro-imaging analysis

After freezing, the skin explants were cut longitudinally using a Cryotome with a thickness of 20 μm .

For each explant, 3 tissue sections were selected and deposited on a CaF_2 support for Raman imaging analysis. In total 9 images Raman (3 sections per explant ($n = 3$) and one image per section) have been recorded.

3 other adjacent sections of 5 μm thickness were prepared for Hematoxylin Eosin (HE) staining.

Raman images had a size of Y: 10 μm / X: 100 μm with a step of 5 μm in X and 5 μm in Y. Each Raman image had 3 Y spectra and 21 X spectra (63 spectra per image).

The following Raman image acquisition parameters were used:

- Laser wavelength: 660 nm (Xplora)
- Lens: 100 X, long focal length
- Acquisition time: 20 seconds
- Accumulation: 1X
- Spectral range: 500 to 3600 cm^{-1}
- Grating: 600T
- Confocal Hole: 300 μm
- Slit width: 100 μm
- Step in X: 5 μm , Step in Y: 5 μm

In order to ensure reproducibility of the measurements, the Raman spectrometer is calibrated with silicon (peak at 520.7 cm^{-1}) prior to each use. Also, continuous control of the laser power at the sample level was achieved.

The Raman images were pre-processed by elimination of aberrant spectra (fluorescence, burning, saturation...), correction of baseline, spectral smoothing and despiking, and spectra normalization.

The Raman spectral images were analyzed by Fitting. This analysis consists of a mathematical modeling of the reference spectra in the global spectral image to determine the contribution and distribution of these spectra within the image. The spectra of samples D and E, as well as of the untreated condition, were used as reference spectra.

It was further checked that Raman signature of retinol can be detected both for samples D and E:

- Samples D and E give Raman spectra with characteristic peaks and no auto-fluorescence problem with 660 nm laser excitation in the spectral range from 500 to 3600 cm^{-1} .
- The Raman spectra of samples D and E have a different spectral signature.
- The specific markers of retinol (peaks at 1158, 1197 and 1594 cm^{-1}) can be detected for both samples.

The comparison of the Raman spectra of samples D and E, respectively, with the reference spectrum of the skin (untreated skin control) allows the identification of spectroscopic markers specific to retinol products and which can be used to track their penetration and distribution at skin sections.

These Raman markers were then used to determine the skin penetration of samples D and E, respectively, after 8 hours and 7 days of topical application.

All results are presented with the mean image ($n = 3$) showing the distribution of the reference spectrum of sample D or E in the epidermis after 8 hours (Figure 4) and 7 days (Figure 5), respectively.

Results of Experiment 1 (8 hours):

Raman signal for retinol was found on the skin treated with sample E, but was very low for sample D.

Thus, it was evidenced that the multilayer crystalline microcapsules of the present invention showed a skin penetration on the epidermis layer after 8 hours of topical application.

Moreover, the Raman signal obtained with sample E showed retinol detection until 30 μm of depth in the epidermis.

Thus, the multilayer crystalline microcapsules of the present invention showed a high transcutaneous penetration after 8 hours of topical application, which was better and more effective than that of free retinol.

Results of Experiment 2 (7 days):

Raman signal for retinol was found more prominently on the skin treated with sample E than with sample D after 7 days of topical application.

Sample D showed a slight penetration in the epidermis layer with retinol detection at 30 μm of depth and mainly located in the stratum corneum.

- 5 Sample E showed a good transcutaneous penetration of retinol after 7 days of topical application. Indeed, retinol from sample E was detected at 150 μm of depth with an important accumulation in the stratum corneum.

Thus, the multilayer crystalline microcapsules of the present invention evidenced a better transcutaneous penetration of retinol than free retinol after 7 days of topical application.

10 Example 9: Skin Irritation Test (Clinical Study)

To evaluate possible irritating effects on the human skin, an occlusive patch test was conducted.

Materials

The following two samples were tested:

F. Placebo composition of example 6

- 15 G. Retinol-containing multilayer crystalline microcapsules from example 1 at a concentration of 3 wt% in the placebo composition of example 6 (resulting in a concentration of 0.3 wt% of pure retinol)

Methodology

- 20 The epicutaneous patch test allows to assess the primary skin irritation potential of cosmetic finished product and raw materials.

The study was conducted considering the guidelines by COLIPA (Walker A:P: et al: Test Guidelines for Assessment of Skin Compatibility of Cosmetic Finished Products in Man. Food and Chemical Toxicology 34, 1996, 651-660: COSMETICS EUROPE: Product test guidelines for the assessment of human skin compatibility 1997). In addition, it was carried out taking into account the principle requirements of the Declaration of Helsinki (1964) and subsequent revisions.

25

Experiments were carried out on 50 volunteers (28 normal healthy subjects, 4 eczema patients, 2 allergy patients, 16 subjects with sensitive skin) between the ages of 18 to 72. Sex distribution was not standardized. The volunteers were clearly informed, verbally and in writing, regarding the nature of the study, the timetable, constraints and possible risks. They gave their written informed consent before participating in the study. Participants could withdraw from the study at any time without giving reason. During the test period, the volunteers refrained from using other substances on the test areas.

The samples were applied in the concentrations as outlined above in square test-chambers (allergEAZE® clear Patch Test Chambers; Smart Practice®, Phoenix, AZ) to the back of the volunteers for a period of 48 hours. Proper adherence of the test patches was assured by the inclusion of sodium dodecyl sulphate (SDS) at a concentration of 1% as a positive control. Water was used as a negative control.

The treatment sites were assessed for the presence of irritation by a trained evaluator using a 5-point visual scoring scale at 48 h (30 min after patch removal) and 72 h after patch application.

The following scoring scale was used:

	0	1	2	3	4
Erythema	No	Slight	Significant	Pronounced	Strong
Fissure	No	Minimal	Significantly perceptible	Pronounced	Ulceration
Scaling	No	Minimal	Moderate	Significant	Closed scale crust

Results

For the negative control (water), the score was 0 for each volunteer in all three conditions and at both time points.

For the positive control (1% SDS in water), some slight to clear erythema and minimal to clearly visible scaling was observed, but no fissure:

	After 48 hours			After 72 hours		
	Erythema	Fissure	Scaling	Erythema	Fissure	Scaling
Normal skin (28)	25x0 2x1 1x2	All 0	27x0 no 1 1x2	26x0 1x1 1x2	All 0	27x0 1x1 no 2

Eczema (4)	1x0 2x1 1x2	All 0	1x0 3x1 no 2	1x0 2x1 1x2	All 0	2x0 2x1 no 2
Allergy (2)	All 0	All 0	All 0	All 0	All 0	All 0
Sensitive skin (16)	9x0 5x1 2x2	All 0	13x0 2x1 1x2	9x0 5x1 2x2	All 0	13x0 2x1 1x2
Average score	0.34	0.00	0.18	0.32	0.00	0.14

For sample F (placebo), the score was 0 for each volunteer in all three conditions and at both time points.

For sample G (present invention), some slight erythema was observed, but no fissure nor scaling:

	After 48 hours			After 72 hours		
	Erythema	Fissure	Scaling	Erythema	Fissure	Scaling
Normal skin (28)	All 0	All 0	All 0	All 0	All 0	All 0
Eczema (4)	3x0 1x1 no 2	All 0	All 0	3x0 1x1 no 2	All 0	All 0
Allergy (2)	All 0	All 0	All 0	All 0	All 0	All 0
Sensitive skin (16)	15x0 1x1 no 2	All 0	All 0	All 0	All 0	All 0
Average score	0.04	0.00	0.00	0.02	0.00	0.00

By consequence, sample G was classified as “harmless” as regards the possibility of skin irritation.

Example 10: Anti-Aging Activity (Clinical Study)

- 10 To evaluate the anti-ageing benefits of retinol-containing multilayer crystalline microcapsules of the present invention compared to free retinol in face care applications, a clinical test was

conducted on 40 women presenting crow's feet wrinkles and nasolabial wrinkles in double blind versus placebo test.

In this manner, the anti-aging activity of the skin care compositions of examples 4, 5 and 6 were investigated.

5 *Panel description*

The panel consisted of 40 female volunteers having wrinkles on crow's feet and nasolabial area in double blind versus placebo test. Volunteers were informed of the possible adverse effects from using the compositions and the technical conditions in which the assessment is performed. They willingly signed the consent form which was written in compliance with the Declaration of Helsinki and the December 20th, 1988 act of the Code de la Santé Publique.

Volunteers were divided in two groups as presented below:

- Group 1: 20 women (54 ± 5 years old) applied the composition of example 4 on one hemi-face and the placebo composition of example 6 on the other hemi-face for 56 days.
- Group 2: 20 women (54 ± 7 years old) applied the composition of example 4 on one hemi-face and the comparative composition of example 5 on the other hemi-face for 56 days.

The skin care compositions were packed into a dark packaging and were applied once a day (only in the evening) for 56 days. The anti-aging properties were evaluated after 28 days and 56 days of application using VISIA CR 2.3® and AEVA-HE®.

With VISIA® 6th generation, numeric photographs of the face were performed. For each volunteer and time point, two photos are taken: right profile and left profile. These photos were then analyzed using Visia CR 2.3® to determine the number of wrinkles and the skin texture (microrelief of the skin, smoothness or roughness).

AEVA-HE® was used to analyze the wrinkles depth and volume in the nasolabial area. AEVA-HE® is a high resolution 3D measurement system for skin topography, face topology and body morphology changes, which is based on a fringe projection unit combined with stereo imaging techniques, and which is commercially available from EOTECH SAS (<http://eotech-sa.com/life->

science/3d-sensors/aeva-he/ and http://eotech-sa.com/wp-content/uploads//2018/09/AEVA-HE_web.pdf).

Volunteers were also asked to complete a self-assessment questionnaire after 55 days of product application.

5 RESULTS

Impact on the number of wrinkles and skin texture on the crow's feet:

A significant reduction of the number of wrinkles by -17.1% ($p < 0.001$) and -11% ($p < 0.01$) was observed with the composition of example 4 relative to D0 after 28 days and 56 days of application, respectively.

- 10 In addition, a significant decrease of the number of wrinkles was shown relative to the placebo composition of example 6, with -11.1% ($p < 0.1$) and -13.3% ($p < 0.05$) at D28 and D56, respectively.

The reduction of the number of wrinkles was not significant with the comparative composition of example 5 at either time point, nor was it with the placebo composition of example 6.

- 15 It was further demonstrated that the composition of example 4 is significantly more efficient than the comparative composition of example 5, as observed by the significant difference in the number of wrinkles between the two compositions of -8.7% ($p < 0.05$) and -5% ($p < 0.05$) after D28 and D56, respectively.

The skin texture was analyzed using VISIA analysis.

- 20 It was evidenced that the composition of example 4 induced a relevant improvement of skin texture relative to D0 with -12.1% ($p < 0.001$) and -3.4% after D28 and D56, respectively.

The improvement of skin texture was not significant with the comparative composition of example 5 at either time point, nor was it with the placebo composition of example 6.

- 25 Moreover, it was shown that the composition of example 4 induced a significant improvement of skin texture in comparison with the placebo composition of example 6, with -11.9% ($p < 0.05$) and -9.5% ($p < 0.1$) after D28 and D56 of application, respectively.

It was further observed that the composition of example 4 is more efficient than the comparative composition of example 5, which showed only a slight skin texture improvement of -5.5% and -1% relative to D0 after D28 and D56 of application, respectively.

Impact on depth and volume on nasolabial wrinkles:

- 5 It was found that the composition of example 4 led to a reduction of the wrinkles' volume relative to D0 by -11.5% ($p < 0.05$) and -23.4% after D28 and D56, respectively.

Moreover, a significant difference relative to the placebo composition of example 6 was demonstrated, with a reduction of wrinkles volume by -37.3% ($p < 0.05$) after D56 of application with the composition of example 4.

- 10 The placebo composition of example 6 lead to an increase in wrinkles' volume by +13.9% ($p < 0.1$) after D56 of application.

The comparative composition of example 5 showed a slightly lower effect than the composition of example 4, with only a reduction of the wrinkles' volume by -12.1% ($p < 0.1$) after D56 of application.

- 15 It was further found that the composition of example 4 induced a reduction of wrinkles' depth in the nasolabial area relative to D0 by -4.3% and -11.3% after D28 and D56 of application, respectively.

- In addition, a significant difference between the composition of example 4 and the placebo composition of example 6 on the reduction of wrinkles' depth after D56 of application was
20 shown, with -18.4% ($p < 0.05$).

The placebo composition of example 6 lead to an increase in wrinkles' depth by +7.1% ($p < 0.1$) after D56 of application.

The comparative composition of example 5 did not exhibit any effect on the wrinkles' depth in the nasolabial area relative to D0 nor to the placebo composition of example 6.

Claims

1. Cosmetic ingredient comprising multilayer crystalline microcapsules comprising retinol.
2. Cosmetic ingredient according to claim 1, wherein the multilayer crystalline microcapsules comprise 15 to 75 wt% of non-ionic surfactants, more preferably 15 to 50 wt% of non-ionic surfactants, and most preferably about 20 wt% of non-ionic surfactants.
3. Cosmetic ingredient according to claim 2, wherein the non-ionic surfactants are selected from the group consisting of cetostearyl alcohol, a polysorbate, glyceryl linoleate, docosan-1-ol, sorbitan monostearate, and mixtures thereof.
4. Cosmetic ingredient according to claim 3, wherein the non-ionic surfactants consists of a mixture of cetostearyl alcohol and polysorbate 60, preferably in a ratio of 4:1 to 1:1.
5. Cosmetic ingredient according to any one of the preceding claims, wherein the multilayer crystalline microcapsules have an average diameter of 0.3 to 100 μm , more preferably of 1 to 50 μm , and most preferably of 2 to 30 μm .
6. Cosmetic ingredient according to any one of the preceding claims, wherein the multilayer crystalline microcapsules comprise 1 to 15 wt% of retinol, more preferably 5 to 12 wt% of retinol, and most preferably about 10 wt% of retinol.
7. Cosmetic ingredient according to any one of the preceding claims, further comprising a polar solvent, preferably a polar solvent selected from the group consisting of water, glycerine, 1,3-propanediol, and mixtures thereof.
8. Cosmetic ingredient according to any one of the preceding claims, further comprising and antioxidant, preferably an antioxidant selected from the group consisting of butylated hydroxytoluene, butylated hydroxyanisole, and mixtures thereof.
9. Cosmetic composition comprising the cosmetic ingredient according to any one of the preceding claims and a cosmetically acceptable excipient.
10. Skin care composition according to claim 9, in particular an anti-aging skin care composition.

11. Method of reducing the signs of aging in skin, comprising the step of applying the cosmetic active agent according to any one of claims 1 to 7 or the cosmetic composition according to claim 8 or 9 to the skin, in particular to facial skin.
12. Method according to claim 11, wherein wrinkles are reduced.
- 5 13. Method of stabilizing retinol, comprising the step of preparing multilayer crystalline microcapsules comprising retinol.
14. Method of reducing skin irritation of retinol, comprising the step of preparing multilayer crystalline microcapsules comprising retinol.

1 / 5

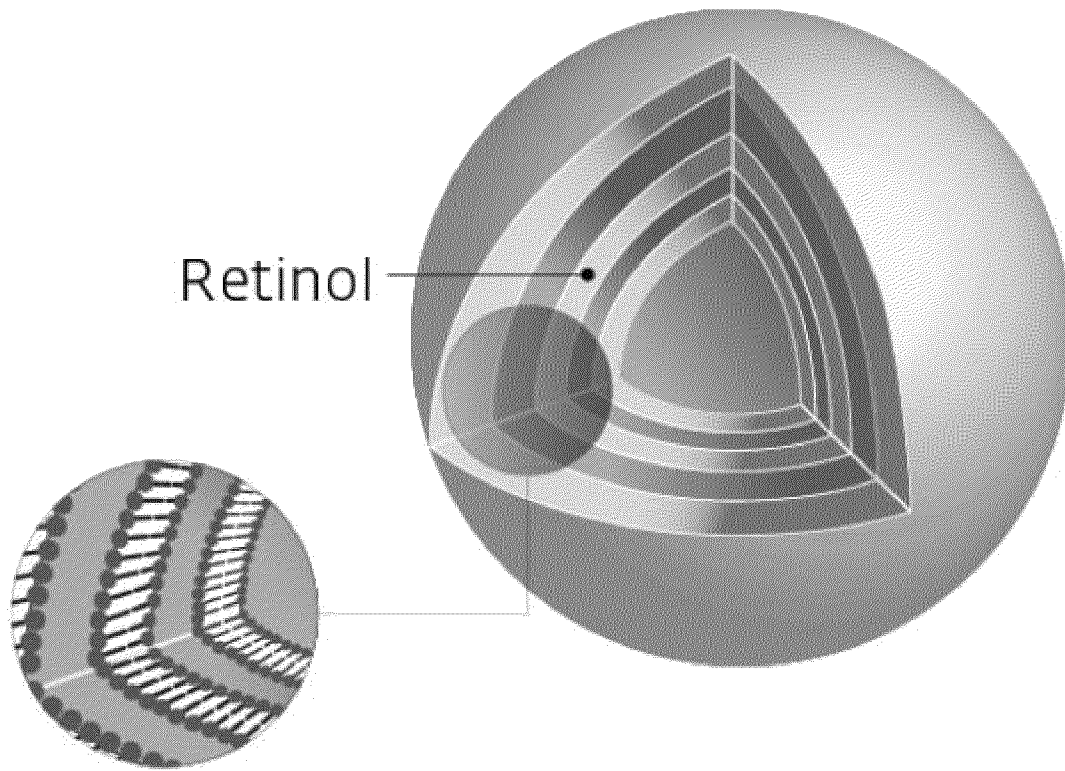


Figure 1

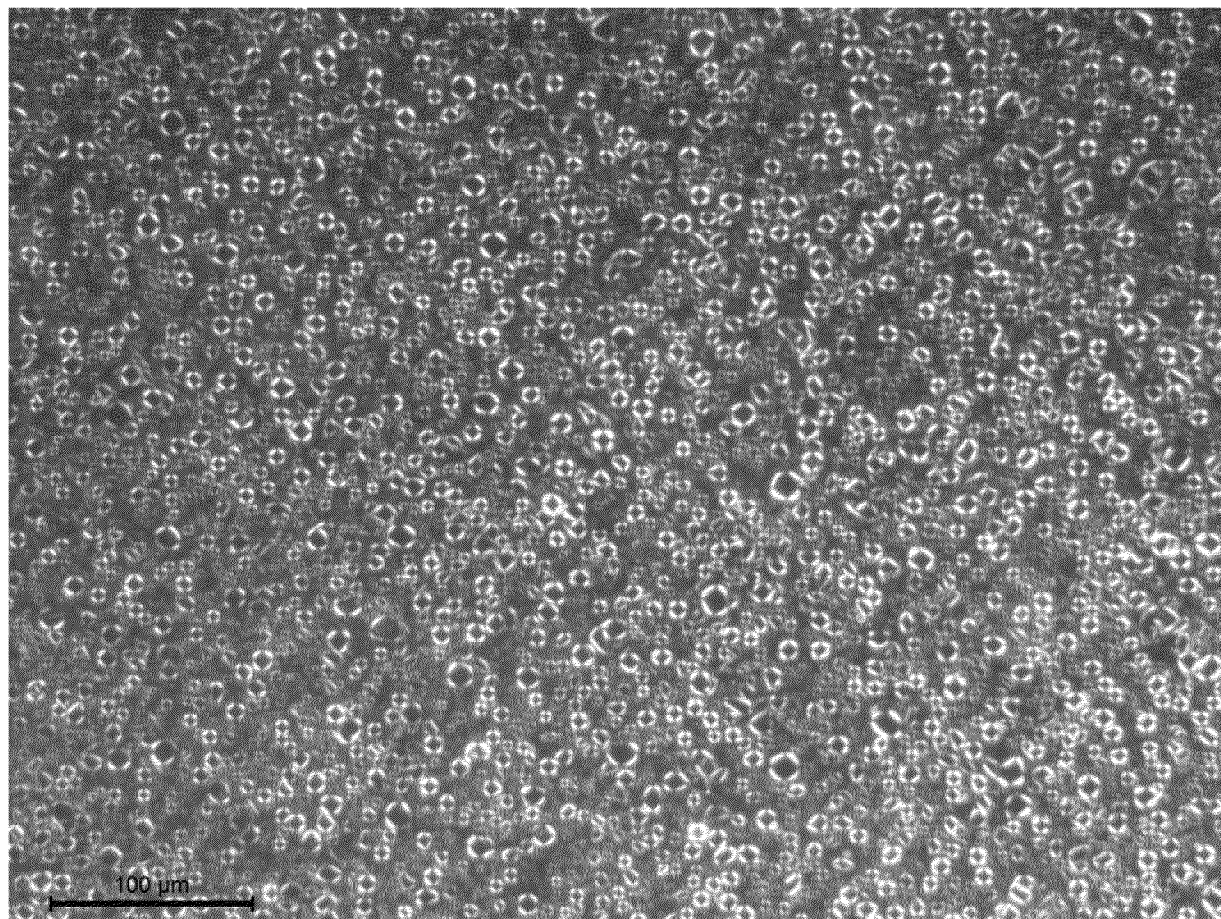


Figure 2

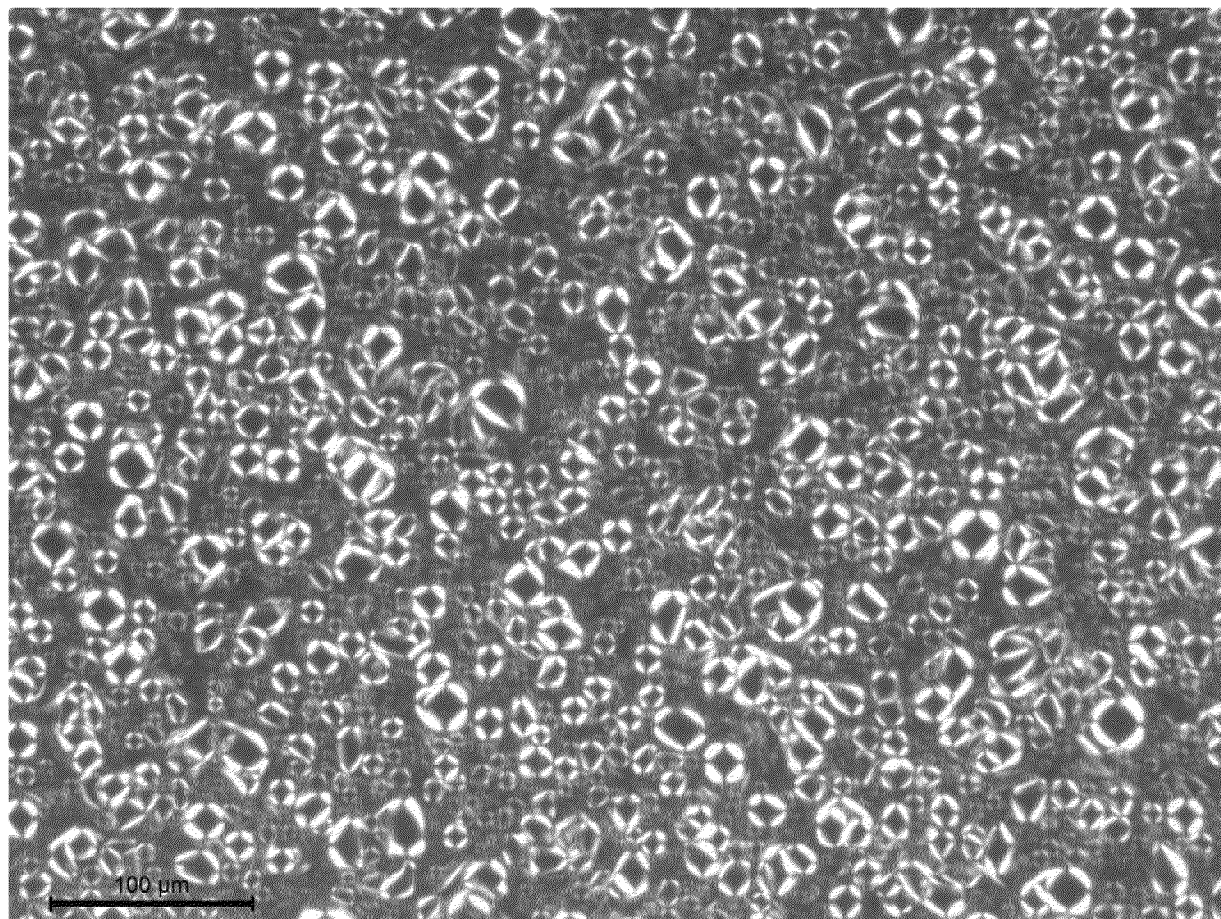


Figure 3

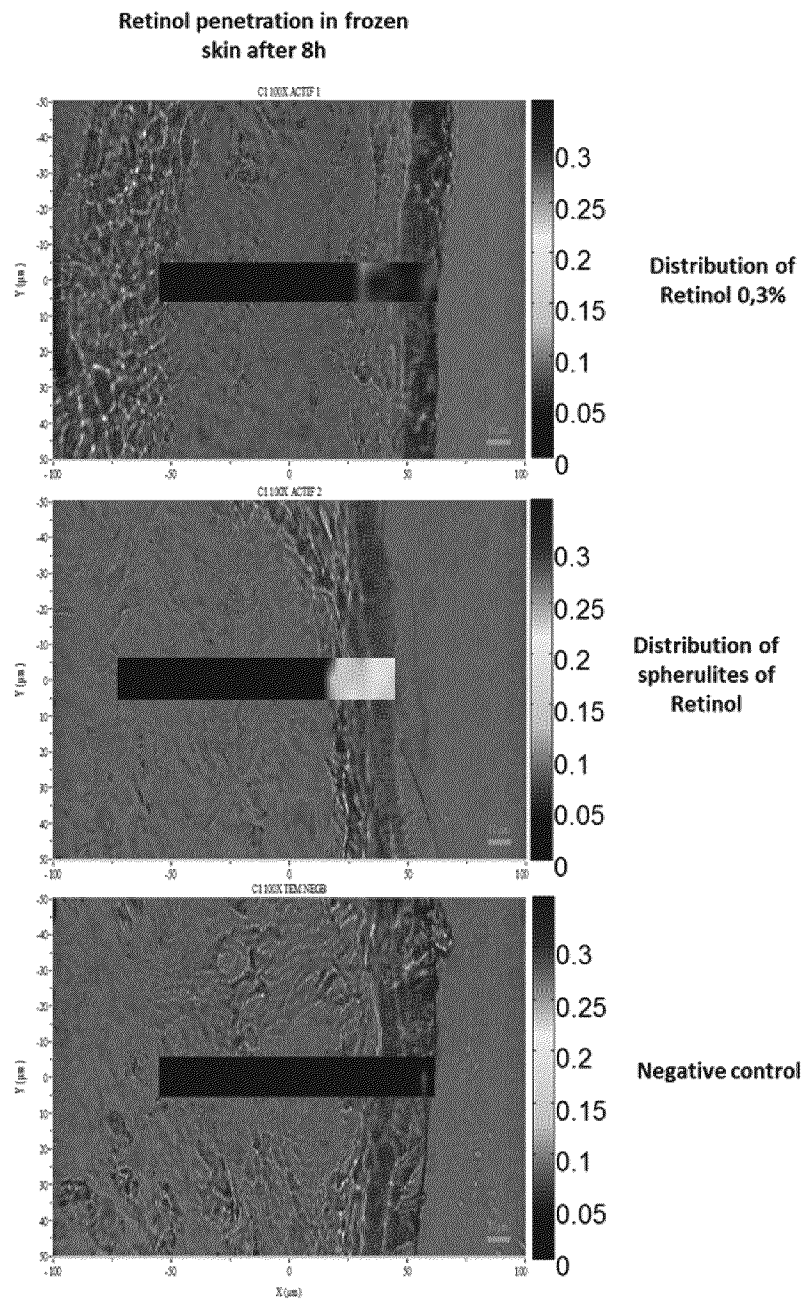
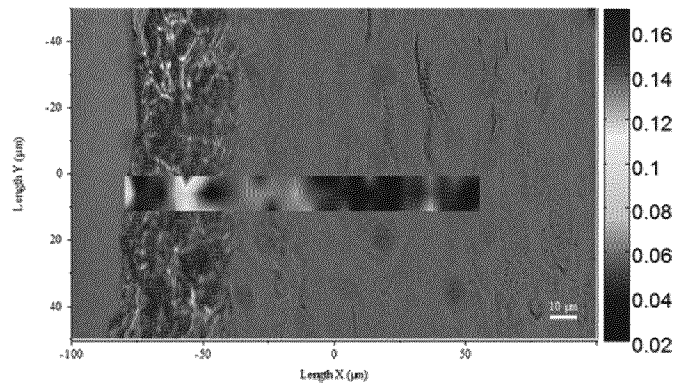


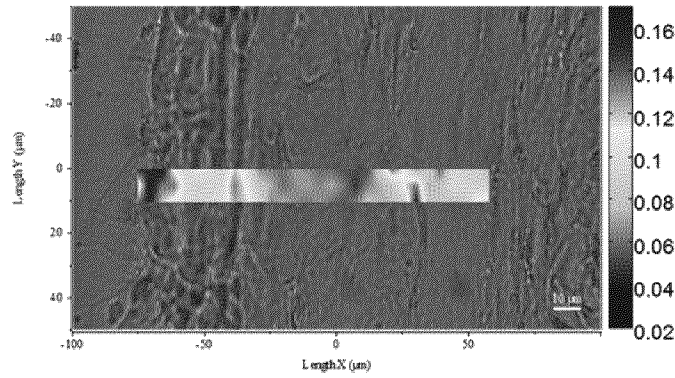
Figure 4

Retinol penetration in fresh skin
maintained in survival after 7D

Distribution of
Retinol 0,3%



Distribution of
spherulites of
Retinol



Negative control

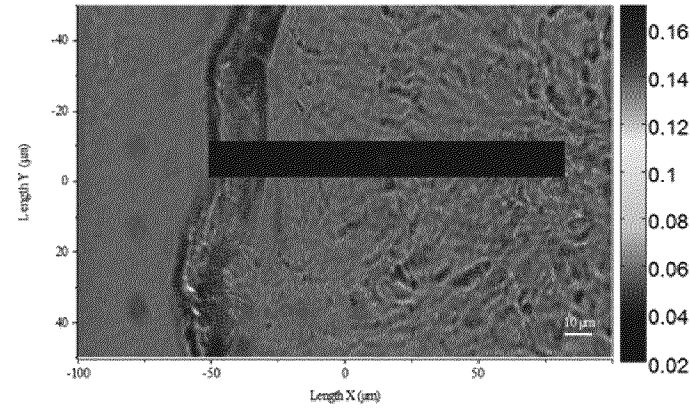


Figure 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/062369

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61Q19/08 A61K8/11 A61K8/14 A61K8/34 A61K8/49
A61K8/67

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 June 2020

Date of mailing of the international search report

08/07/2020

Name and mailing address of the ISA/

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Diebold, Alain

INTERNATIONAL SEARCH REPORT

International application No
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