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(71) Applicant(s)
Ego Pharmaceuticals Pty Ltd

(72) Inventor(s)
Greive, Kerryn;Heinicke, Ingrid

(74) Agent / Attorney
FPA Patent Attorneys Pty Ltd, Level 43 101 Collins Street, Melbourne, VIC, 3000, AU

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(71) Applicant: **EGO PHARMACEUTICALS PTY LTD** [AU/AU]; 21-31 Malcolm Road, Braeside, Victoria 3195 (AU).

(72) Inventors: **GREIVE, Kerryn**; c/- 21-31 Malcolm Road, Braeside, Victoria 3195 (AU). **HEINICKE, Ingrid**; c/- 21-31 Malcolm Road, Braeside, Victoria 3195 (AU).

(74) Agent: **FREEHILLS PATENT ATTORNEYS**; Level 43, 101 Collins Street, Melbourne, Victoria 3000 (AU).

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(54) Title: COMPOSITIONS THAT ASSIST SKIN HEALING AND/OR MAINTAIN SKIN HEALTH

(57) Abstract: The present invention relates to compositions that assist skin healing and/or maintain skin health. The invention also relates to methods for increasing collagen in the skin and methods for treating or preventing the development or recurrence of erythema. The compositions according to the present invention comprise disodium lauriminodipropionate tocopheryl phosphates and, preferably, one or more anti-irritants and one or more vitamins.

Compositions that assist skin healing and/or maintain skin health

Field of the invention

The present invention relates to compositions that assist skin healing and/or maintain skin health, such as increasing collagen in the skin and/or treatment or prevention of the development or recurrence of erythema. In addition, the present invention relates to a method for assisting skin healing and/or maintaining skin health.

Background of the invention

There are many causes of damage to the skin and many of these results in erythema. Erythema is a skin condition characterised by abnormal redness of the skin. It is a medical condition that is more significant than the normal flushed cheeks and/or nose in the fair and sensitive skinned.

Erythema can occur in various skin conditions such as eczema, psoriasis and rosacea. It is a condition associated with inflammation of the skin and can be caused by external irritation of the skin, for example, by over exposure to the sun or contact with irritating substances such as plants (eg poison ivy), various chemicals and some metals (eg nickel in jewellery). Erythema can also occur when the skin is damaged by piercing with an object or following an insect bite. This damage can be unintentional or an intended part of a procedure such as skin needling. Erythema may also occur following various medical and cosmetic procedures including laser treatment, intense pulsed light (IPL) treatment and microdermabrasion. Erythema may occur in response to an allergic reaction or an infection. It is a common side effect of radiotherapy treatment and can be a side effect of medication or an illness. As a final example, erythema may occur as a side effect of certain types of poisoning including vitamin A toxicity. Despite the numerous known causes of erythema, in a significant proportion of cases the cause of erythema is unknown.

Traditional treatments include antibiotics such as doxycycline. Alternative oral treatments include vitamin A medications, such as isotretinoin, steroids and antifungal medications. These treatments have significant side effects, for example isotretinoin has

teratogenic side-effects. Antibiotics, antifungals and steroids can be administered topically but have limited efficacy and/or restrictions on use due to safety concerns. Other topical treatments include metronidazole, azelaic acid, retinoic acid/retinaldehyde, and vitamin C.

There are also light therapies to treat erythema, particularly erythema associated with rosacea and laser treatments involving the ablation of blood vessels.

1% hydrocortisone as a topical cream is one of the common short-term topical treatments for erythema.

There are limitations to all of the current treatments either with efficacy or toxicity. Erythema, particularly erythema associated with rosacea, can be a persistent and chronic condition involving repeated remission and exacerbation. Many of the treatments such as steroids or antibiotics are not appropriate for long term use. There is a need for a non-prescription, non-steroid product that effectively assists the skin to heal and, in particular, treats erythema. The minimisation of side-effects is particularly important because some conditions associated with erythema, such as rosacea, often require lifelong symptomatic treatment. In addition, the subject's skin may be so sensitive that many topical products are irritating. If a treatment is not sufficiently mild, it can exacerbate rather than improve the symptoms. A better treatment in these cases is one that is effective, mild and can be used long term.

WO 2002/74290 describes treatment of rosacea with a non-steroidal anti-inflammatory drug such as piroxiam, aspirin, ibufenac or naproxen in combination with nitroimidazole.

WO 2009/150257 discloses compositions for treating rosacea containing chitosan, a chitosan derivative or a physiologically acceptable salt thereof and a short-medium chain dicarboxylic acid amide.

Brimonidine was reported as useful in the topical treatment of erythema in WO 2011/117377, WO 2012/112566 disclosed cream compositions of oxymetazoline for treating symptoms of rosacea including erythema, and WO 2012/047645 disclosed the topical treatment of rosacea with a combination of brimonidine and oxymetazoline.

WO 2011/000218 disclosed the topical treatment of rosacea with berberine or a biologically equivalent analogue thereof. WO 2012/001053 disclosed treatment of rosacea with metronidazole esters.

The majority of the dermis of the skin is collagen. The collagen both supports the skin structure and retains moisture. Collagen fibres in the skin are reduced by exposure to ultraviolet radiation, a dry environment and oxidation. The amount of collagen in the skin also reduces with age. Reduction of collagen is associated with reduced resilience and elasticity in the skin. Increased collagen production improves skin healing in patients with erythema. In addition, maintenance and/or increases in collagen levels in the skin assist to maintain skin function and appearance. Overtime, this may prevent aging or have an antiaging effect.

Retinoids are known to increase collagen production. However, they have high photoreactivity and require protection from light for stable storage. Retinoids also have significant incidence of adverse reactions including photosensitisation of the skin, which makes skin more susceptible to sunburn.

WO 2012/108410 discloses the use of TGF-β and/or TGF-β degradation products in the induction of collagen in the skin. WO 2011/040363 discloses a composition for promoting collagen production comprising one or more of D-aspartic acid, D-alanine and derivatives and/or salts thereof. WO 2005/034902 describes a composition for promoting collagen production comprising one or more purine nucleic acid-related substances.

Reference to any prior art in the specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in Australia or any other jurisdiction or that this prior art could reasonably be expected to be ascertained, understood and regarded as relevant by a person skilled in the art.

Summary of the invention

The inventors of the present invention developed topical formulations intended as soothing products for sensitive skin types, that is, to soothe sensitive but undamaged skin. The formulations are intended to desensitise the skin by hydration and moisturisation. Surprisingly, the inventors discovered that the formulations of the invention have an additional and unexpected effect on healing damaged and inflamed skin with erythema. In addition, the formulations of the invention have been found to increase the amount of collagen in the skin, which further assists with skin healing. In addition, the increase in collagen may protect the skin from degradation due to aging and/or provide an anti-ageing benefit.

In one aspect, the present invention provides a method of increasing collagen in the skin of a subject comprising topical administration of a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphates. In an alternate aspect, the present invention provides a method of increasing collagen in the skin of a subject comprising topical administration of a physiologically effective amount of a composition comprising hamemalis virginiana water. In a preferred embodiment, the subject is identified as likely to benefit from increased collagen in the skin. The benefit from the increased collagen may be improved healing following skin damage, the prevention or reduction of skin damage from exposure to ultraviolet radiation or during therapeutic or cosmetic procedures such as laser treatment, prevention of aging, maintenance of skin health, or antiaging. The increased production of collagen may occur in any skin cell type. It is particularly beneficial for the increase in collagen to occur in fibroblasts. Where the increased production of collagen occurs in firbroblasts it may also occur in other skin cell types.

A physiologically effective amount of disodium lauriminodipropionate tocopheryl phosphates may be provided in the form of a topical formulation comprising 0.4 to 2% w/w disodium lauriminodipropionate tocopheryl phosphates.

In a preferred embodiment, administration of the composition increases production of collagen III by about 10% or more, for example, when measured by fluorescent antibody binding. In a preferred embodiment, administration of the composition increases

collagen III by about 20% or more and in a most preferred embodiment, administration of the composition increases collagen III by about 40%.

Further, in a preferred embodiment, administration of the composition increases production of collagen I by about 5% or more, for example, when measured by florescent antibody binding. In a particularly preferred embodiment, administration of the composition increases collagen I by about 15%. Alternatively, the composition administered to the subject is a composition that if administered to human foreskin fibroblasts results in about a 40% increase in collagen III and/or about a 15% increase in collagen I after about 60 hours of incubation with the composition.

In all alternative embodiments of the invention the subject can be a human subject.

In a second aspect, the present invention provides a method of treatment, prevention or prevention of recurrence of erythema comprising topical administration of a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphates. In a preferred aspect, the method is a method of treatment. In one embodiment, the subject is identified as having erythema. In an alternate embodiment, the subject is identified as being at risk of developing erythema. In another alternate embodiment, the subject is identified as being at risk of recurrence of erythema. The erythema may be caused by any of the known causes discussed above. The cause of the erythema may be unknown. In one embodiment, the treatment of the erythema is post laser skin treatments, chemical peels, microdermabrasion or skin needling. In another embodiment, the erythema treated is associated with rosacea, psoriasis or eczema. In another embodiment, the method is to prevent recurrence of rosacea.

In a preferred embodiment, the administration of the composition reduced the Standard Scalar Rating for the erythema by 75% or more by 7 days after use. It is preferred if the Standard Scalar Rating is reduced by 80% or more by 7 days after use. In an alternative preferred embodiment, the administration of the composition reduced the Standard Scalar Rating for the erythema by 3.0 or more by 7 days after use. It is preferred if the

Standard Scalar Rating is reduced by 3.3 or more by 7 days after use. The Standard Scalar Rating is explained below.

In an alternative preferred embodiment, the administration of the composition resulted in a magenta to blue shift, ie a* as measured by a Minolta Spectrometer Model CM-2600, of -2.5 or a greater negative by 48 hours after use. It is preferred if the magenta to blue shift is -2.8 or a greater negative by 48 hours after use. In an alternative preferred embodiment, the magenta to blue shift is -4 or a greater negative by 7 days after use. It is preferred if the magenta to blue shift is -4.6 or a greater negative by 7 days after use.

In an alternative preferred embodiment, the administration of the composition results in a ΔE, ie $(\Delta E) = \sqrt{(\Delta L^2 + \Delta a^2 + \Delta b^2)}$ as measured by a Minolta Spectrometer, of 3.5 or more by 48 hours after use. It is preferred if the ΔE is 3.7 or more by 48 hours after use. In an alternative preferred embodiment, the ΔE is 5 or more by 7 days after use. It is preferred if the ΔE is 5.7 or more by 7 days after use.

In a preferred embodiment, the composition of the present invention comprises disodium lauriminodipropionate tocopheryl phosphates, at least one vitamin and at least one anti-irritant. The anti-irritant can be an emollient, a vitamin, an antioxidant or a herbal extract. Vitamin E, liquid paraffin, aloe vera and avena sativa kernel extract are suitable. Avena sativa kernel extract is preferred. The at least one vitamin is preferably nicotinamide. In a particularly preferred embodiment, the composition includes the two vitamins nicotinamide and panthenol.

In a particularly preferred embodiment, the composition of the present invention comprises disodium lauriminodipropionate tocopheryl phosphates, at least one vitamin, at least one anti-irritant and hamemalis virginiana water.

In one embodiment, the composition further includes menthol for a cooling effect. In a particularly preferred embodiment, the composition includes the anti-irritant avena sative kernel extract, the two vitamins nicotinamide and panthenol, and menthol.

The composition of the present invention optionally further includes one or more emulsifiers, emollients, thickeners, humectants, preservatives, body builders, pearlizing agents, bulking agents, pH adjusters, feel modifiers, colouring agents and/or fragrances.

The composition of the invention can be a cream, lotion or gel.

In one aspect, the composition of the invention comprises:

a. disodium lauriminodipropionate tocopheryl phosphate in an amount equivalent to 1 to 5 percent (w/w) of a 40% active composition;
b. in combination with one or more of hamemalis virginiana water 0.5 to 10 percent (w/w);
c. nicotinamide 0.5 to 5 percent (w/w);
d. avena sativa kernel extract in an amount equivalent to 0.5 to 5 percent (w/w) of a 100 ppm solution; and
e. menthol 0.01 to 0.1 percent (w/w).

Where the disodium lauriminodipropionate tocopheryl phosphate in the above composition is in a form comprising 40% (w/w) active ingredient, that form is 1, 2, 3, 4 or 5 percent (w/w) of the composition. More preferably, the disodium lauriminodipropionate tocopheryl phosphate in the above composition is in a form comprising 40% active ingredient and that form is 3 percent (w/w) of the composition. Where the disodium lauriminodipropionate tocopheryl phosphate is not in a form comprising 40% active, the active is preferably 1.2% (w/w) of the above composition.

The avena sativa kernel extract may be a 100 ppm solution. When in a 100 ppm solution it is preferred that solution is 0.5 to 5 percent (w/w) of the composition and most preferred that the solution is 1 percent (w/w) of the composition. Where the avena sativa kernel extract is in another form it is preferred that the active in the extract is in an amount equivalent to the amounts stated above.

In one embodiment, the disodium lauriminodipropionate tocopheryl phosphate is in combination with both the avena sativa kernel extract and the menthol. In an alternative embodiment, the disodium lauriminodipropionate tocopheryl phosphate is in combination with both the avena sativa kernel extract and the nicotinamide. In an

alternative embodiment, the disodium lauriminodipropionate tocopheryl phosphate is in combination with both the avena sativa kernel extract and the hamemalis virginiana water. In a preferred embodiment, the disodium lauriminodipropionate tocopheryl phosphate is in combination with the avena sativa kernel extract, the menthol and the hamemalis virginiana water.

In a preferred embodiment, the hamemalis virginiana water is in combination with all of the four ingredients listed in the paragraph directly above. In this embodiment, the proportions are desirably:

disodium lauriminodipropionate tocopheryl phosphates 3.00 percent (w/w) in the form of a 40% active composition;

hamemalis virginiana water 3 percent (w/w);

avena sativa kernel extract in a 100 ppm solution 1 percent (w/w);

nicotinamide 1 percent (w/w); and

menthol 0.03 percent (w/w).

Alternatively, the proportions are desirably:

disodium lauriminodipropionate tocopheryl phosphates 1.2 percent (w/w);

hamemalis virginiana water 3 percent (w/w);

avena sativa kernel extract in an amount equivalent to 1 percent (w/w) of a 100 ppm solution;

nicotinamide 1 percent (w/w); and

menthol 0.03 percent (w/w).

In a preferred embodiment, the composition consists essentially of:

a. disodium lauriminodipropionate tocopheryl phosphates 1.2 percent (w/w);

b. hamemalis virginiana water 3 percent (w/w);
c. avena sativa kernel extract in an amount equivalent to 1 percent (w/w) of a 100 ppm solution;
d. nicotinamide 1 percent (w/w);
e. menthol 0.03 percent (w/w);
f. one or more humectants, emollients, thickeners, emulsifiers, preservatives, surfactants, pH adjustors, pearling, colouring or sent agents; and
g. water q.s..

In a further aspect, the present invention provides the use of a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphates in the preparation of a medicament for increasing collagen in the skin of a subject. It is preferred, that the medicament is also for the topical treatment or prevention of the development or recurrence of erythema.

In a further aspect, the present invention provides a composition comprising a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphates when used to increase collagen in the skin of a subject. It is preferred, that the composition is also used in the topical treatment or prevention of the development or recurrence of erythema.

In a further aspect, the present invention provides the use of a composition comprising a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphates for increasing collagen in the skin of a subject. It is preferred, that the use is also for the topical treatment or prevention of the development or recurrence of erythema.

The exemplified composition may be presented in a container with a pump dispenser. The amount dispensed from the pump can vary but is about 200 milligrams with a fixed % of active as described above. One pump may supply a physiologically effective amount of about 2.5 mg disodium lauriminodipropionate tocopheryl phosphates for application to the face. However, multiple pumps from the dispenser may also be

applied, for example, 2, 5 or 10 pumps to provide a physiologically effective dose to a greater area of skin or to increase the amount of product used on the same area of skin.

Without wishing to be bound by theory or mode of action, it is considered that the increase in the collagen in the skin in combination with the anti-inflammatory effect caused by topical administration of the compositions of the invention causes the treatment or prevention of the development or recurrence of erythema.

Detailed description of the embodiments

It will be understood that various terms employed in the specification, examples and claims have meanings that will be understood by one of ordinary skill in the art. However, certain terms are defined below.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

The term "composition" as used throughout the specification is understood to mean a composition comprising a therapeutically effective amount of at least one therapeutic agent and at least one pharmaceutically acceptable carrier, excipient, diluent, additive or vehicle consistent with the intended form of topical administration and consistent with conventional pharmaceutical practices.

The term "disodium lauriminodipropionate tocopheryl phosphates" as used throughout the specification is understood to mean a blend of tocopherol phosphates with disodium lauriminodipropionate having the International Nomenclature of Cosmetic Ingredients (INCI) name "disodium lauriminodipropionate tocopheryl phosphates".

The term "hamemalis virginiana water" as used throughout the specification is understood to mean a witch hazel distillate, in particular, the witch hazel distillate having the International Nomenclature of Cosmetic Ingredients (INCI) name Hamemalis Virginiana (Witch Hazel) Water.

The term "therapeutic agent" or simply "agent" or "active" as used throughout the specification are understood to mean any substance that is intended for the diagnosis, cure, mitigation, treatment, prevention or modification of a state in a biological system.

The term "physiologically effective" as used throughout the specification relates to the amount or dose of an active agent or a composition thereof that will lead to the desired physiological effect, in particular, the reduction or treatment of erythema, prevention of the development or recurrence of erythema or increase in collagen production in the skin. A physiologically effective amount will vary according to factors such as the severity of the condition, age, gender, and skin type of a subject, and the ability of the substance to elicit a desired response in the subject.

The term "Cetereth-20" as used throughout the specification relates to a polyethylene glycol ether of cetyl alcohol. Its synonyms include Ceteareth-20, Cetomacrogol 1000; PEG-20 cetyl ether; PEG-20 hexadecyl ether; polyethylene glycol 1000 cetyl ether; polyoxyethylene (20) cetyl ether.

The term "panthenol" as used throughout the specification includes "dexpanthenol".

The term "prevention" as used throughout the specification means to inhibit, minimise, defer or delay the onset of a condition.

The composition according to the present invention comprises a physiologically effective amount of disodium lauriminodipropionate tocopheryl phosphates. In one embodiment, the compositions according to the present invention comprise disodium lauriminodipropionate tocopheryl phosphates (40% active) in an amount of about 0.5 to 10 percent (w/w). In a preferred embodiment, the compositions according to the present invention comprise disodium lauriminodipropionate tocopheryl phosphates (40% active) in an amount of about 1 to 5 percent (w/w) or comprise disodium lauriminodipropionate tocopheryl phosphates active in an amount of about 0.5 to 2 percent (w/w). In a particularly preferred embodiment, the composition comprises about 3 percent (w/w) disodium lauriminodipropionate tocopheryl phosphates (40% active) or 1.2 percent (w/w) active disodium lauriminodipropionate tocopheryl phosphates .

The composition of the invention can be a cream, lotion or gel. In a preferred embodiment, the composition according to the present invention further comprises at least one emulsifier. Emulsifiers suitable for use in pharmaceutical compositions are well known to those of ordinary skill in the art and include, for example, polyoxyethylene derivative of sorbitan monolaurate such as polysorbate 20, fatty alcohols such as cetearyl alcohol, ceteareth compounds, and emulsifying waxes. A preferred emulsifier is ceteareth-20, which is commercially available from Croda under the brand name Cetomacrogol 1000.

The amount of emulsifier added to the composition may be readily determined by one of ordinary skill in the art with a minimum of experimentation, and will depend upon factors known to those skilled in the art, such as the properties of the emulsifier and the desired properties of the pharmaceutical composition.

According to one embodiment of the present invention, the composition may include at least one additional "skin active agent". Skin active agents may afford an improvement in the appearance, tone or texture of the skin, and may include, but are not limited to, sunscreens, anti-wrinkling or anti-aging agents, antioxidants, vitamins, depigmentating or skin lightening agents, moisturizing agents, emollients, metal chelators, retinoids and retinoid derivatives, agents intended to reduce skin irritation, and alpha-hydroxy acids.

It will be recognised that the inclusion of skin active agents in the composition according to the present invention will depend upon their physical, chemical and therapeutic compatibility with the other components of the composition.

In one embodiment, the composition according to the present invention further comprises an effective amount of at least one sunscreen. Examples of sunscreens include, but are not limited to, octyl methoxycinnamate, oxybenzone and butyl methoxydibenzoylmethane. Some such sunscreens may retain a more greasy feel but the composition still provides a suitable delivery vehicle for a therapeutic, such as mometasone furoate. In another embodiment the sunscreen is phenylbenzimidazol sulfonic acid or disodium phenyl dibenzimidazole tetrasulfonate or similar.

In one embodiment, the composition according to the present invention may include at least one additional anti-wrinkling or anti-aging agent. Examples of anti-wrinkling or anti-aging agents include, but are not limited to, retinoids (for example, retinoic acid, retinol, retinal, retinyl acetate, and retinyl palmitate), alpha hydroxy acids, galactose sugars (for example, melibiose and lactose), lipoic acid and dihydrolipoic acid, lactoferrin, ascorbic acid, and ascorbic acid derivatives (for example ascorbyl palmitate and ascorbyl polypeptide).

In another embodiment, the composition according to the present invention may include at least one antioxidant or a natural extract that contains antioxidants. Antioxidants may be water or oil-soluble. Oil soluble antioxidants suitable for use in the composition of this invention include, but are not limited to, tocopherols and tocopherol derivatives (for example, tocopheryl acetate, alpha-tocopherol), tocotrienols and ubiquinone. Natural extracts containing antioxidants suitable for use in the composition of this invention, include, but are not limited to, extracts containing flavonoids, phenolic compounds, flavones, flavanones, isoflavonoids, mono-, di- and tri-terpenes, sterols and their derivatives. Examples of such natural extracts include grape seed, green tea, pine bark extracts and legume extracts. Antioxidants may also minimize skin irritation.

In another embodiment, the composition according to the present invention may include at least one agent intended to inhibit or minimise potential skin irritation, such as an emollient (e.g., liquid paraffin), a vitamin, an antioxidant (e.g., vitamin E) and a herbal extract (e.g. aloe vera or avena sativa kernel extract). Avena sativa kernel extract is a preferred anti-irritant.

In another aspect according to the present invention, the composition comprises at least one other component intended to improve the appearance, stability or consumer appeal of the composition. Such components include, but are not limited to: fragrances, emollients, preservatives, vitamins and vitamin derivatives, antioxidants, colours, humectants, plant extracts, surface active agents, and other ingredients to further soothe and protect the skin.

Again, it will be recognised that the inclusion of other components intended to improve the appeal or stability of the composition according to the present invention will depend upon their physical, chemical and therapeutic compatibility with the other components of the composition.

According to the present invention the term 'stability' refers to a composition that does not present any significant macroscopic change of appearance or microscopic change of appearance (e.g. precipitation of an ingredient) over time.

In one embodiment, the composition according to the present invention comprises at least one humectant. Examples of humectants include, but are not limited to: glycerin, glycerol, sodium PCA, panthenol/dexpanthenol, sorbitol, propylene glycol, 1,3-butylene glycol, polypropylene glycol, xylitol, maltitol, lactitol, oat protein, allantoin, acetamine MEA and hylauronic acid.

In another embodiment, the composition according to the present invention may comprise at least one preservative. Examples of preservatives which may be used in the composition of this invention include, but are not limited to, sodium salicylic acid, chlorhexidine hydrochloride, phenoxyethanol, sodium benzoate, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, methyl para-hydroxybenzoate (i.e., methyl paraben), ethyl para-hydroxybenzoate, propyl para-hydroxybenzoate (i.e., propyl paraben) and butyl para-hydroxybenzoate.

In another embodiment, the composition according to the present invention may comprise one or more emollients. Paraffinum liquidum (liquid paraffin), cyclotetrasiloxane and cylclopentasiloxane (Dow Cylcomethicone 345) are suitable emollients.

In another embodiment, the composition according to the present invention may comprise one or more thickeners. Xantham gum and aristoflex AVC (ammonium acryloyldimethyl-taurate/VP copolymer) are suitable thickeners.

In another embodiment, the composition according to the present invention may comprise one or more body builders such as cetearyl alcohol.

In another embodiment, the composition according to the present invention may comprise one or more pearlizing agents such as synthetic fluorophlogopite (and) titanium dioxide (and) tin oxide (Timiron Synwhite 40).

In another embodiment, the composition according to the present invention may comprise one or more bulk agents such as water.

The formulations of the present invention are manufactured in a conventional manner by thoroughly mixing the ingredients at ambient or elevated temperatures.

Any pharmaceutically acceptable acid may be employed to adjust the pH of the pharmaceutical composition of the present invention to a pH suitable for a topical composition. The identity of such acids are known to those of ordinary skill in the art, and include, but are not limited to those described in the International Cosmetic Ingredient Dictionary and Handbook 12th Edition, 2008, Volume 3, pp 3221-3222. Preferred acids are lactic acid, citric acid, hydrochloric acid and sulfuric acid. A particularly preferred acid is citric acid.

The examples that follow are intended to illustrate but in no way limit the present invention.

Example 1 – formulation of the composition

A composition suitable for use in the methods of the present invention can be prepared as follows:

INGREDIENTS	%w/w
Part A: Water Phase	
Purified water	79.605
Glycerin	1.50
Citric Acid	0.34
Dexpanthenol	0.50
Part B: Preservatives	

Sodium methyl paraben	0.25
Sodium propyl paraben	0.15
Part C: Emulsifier	
Ceteareth-20	0.10
Cetearyl alcohol	0.25
Part D:	
Sodium PCA	0.50
Paraffinum liquidum	1.00
Menthol	0.03
Part E:	
Cyclotetrasiloxane and cyclopentasiloxane	3.00
Avena sativa kernel extract (100ppm solution)	1.00
Hamemalis virginiana water	3.00
Nicotinamide	1.00
Part F: Thickener	
Ammonium acryloyldimethyl-taurate/VP copolymer	0.50
Glycerin	3.50
Synthetic fluorophlogopite (and) titanium dioxide (and) tin oxide	0.15
Xanthan Gum	0.625
Part G:	
Disodium lauriminodipropionate tocopheryl phosphate (40% active)	3.00
Total	100.00

Method of formulation:

1. Heat Part A water & citric acid to 60-65°C
2. At 65 °C add Part C and mix until dissolved
3. Add Part D with propeller mixing. Homogenise for 1 minute.
4. Cool batch to 50 °C with propeller mixing.
5. Combine Part A Glycerin and Dexpanthenol and add to batch
6. Add Part E & B with propeller mixing. Homogenise for 30 seconds
7. Combine Part F Glycerin, Xanthan gum and Synthetic fluorophlogopite (and) titanium dioxide (and) tin oxide
8. Add ammonium acryloyldimethyl-taurate/VP copolymer then the rest of Part F to the Batch with propeller mixing
9. Cool batch to 45°C with propeller mixing.
10. Add Part G with propeller mixing
11. Homogenise for 2 minutes.

Example 2 – increase of collagen I and III in the skin

Experimental protocol:

1. Human foreskin fibroblast (HFF) cells were seeded in a 96 well plate. 100µl of cells at $5X10^5$ cells/ml was added per well in Dulbecco's modified eagle medium (DMEM) + 10% fetal calf serum (FCS) + penicillin streptomycin (penstrep).
2. The cells were incubated at 37°C in 5% CO_2 overnight
3. After 24 hrs the cells were transferred serum free media (SFM) for 6 hrs
4. The cell replated with SFM plus in 200µl of the composition formulated in Example 1. SFM alone was used as a control.
5. The cells were left at confluence for 60 hrs to allow collagen to build up
6. The cells were washed 3x with 100µl per well of phosphate buffered saline (PBS)
7. The cells were fixed and permeabilised in ice cold MeOH (-20°C)

8. The fixed cells were transferred to the freezer for 15 minutes

9. The fixed cells were aspirated and air dried briefly then washed 3x with 100µl per well of PBS and treated with Tween 20 (0.5%) in PBS for 10 minutes.

10. The cells were blocked in 50µl per well PBS Tween + 3% normal goat serum (NGS) and incubated in 50µl per well primary antibody in PBS + 3% NGS. For the collagen I experiment the primary antibody was 1:200 Collagen I rabbit polyclonal antibody (Rockland - Cat# 600-401-103.05). For the collagen III experiment the primary antibody was 1:200 Collagen III rabbit polyclonal antibody (Rockland - Cat# 600-401-105.05).

11. The cells were stored at room temperature for 2 hours then washed 3x in 100µl per well PBS and incubated in 50µl per well Alexa conjugated secondary antibody in PBS. The antibody used was 1:200 Alexa 488 goat anti-rabbit IgG (Invitrogen - Cat# A 11008).

12. The cells were stored at room temperature for 1 hour then washed 3x in 100µl per well PBS and 100µl PBS was added to each well.

Analysis:

Analysis was conducted on an Olympus IX81 fluorescence microscope, with Olympus DP80 digital camera and CoolLED light source. In both instances there was a 1.493 second exposure and a 4x gain using the camera set to 0.6MP and with the light path split between the ocular and camera. Images were captured and analysed using cellSens Dimension software (Olympus). Measurements are mean grey scale values of 14 bit images.

Results:

Table 1 - Collagen I

	Blank	SFM	Cells treated with composition of example 1
OD1	1060	7829	8136
OD2	968	7467	8252
OD3	932	6895	8794
OD4	884	7118	7934
OD5	984	7034	8610
OD6	941	7351	8364
OD7	918	7541	7484
OD8	872	7058	
Mean OD	944.875	7287.9	8224.9
Mean OD – mean blank		6343.0	7280.0
SEM		112.2	164.3
P Value v control			0.00066
Mean OD percentage of SFM Mean OD		100%	115%

The results from Table 1 are graphed in Figure 1. The graph shows a significant difference in the collagen I levels in cells treated with serum free medium compared with cells treated with the composition of example 1. The fluorescence for the cells treated with serum free medium was about 6,300, while the fluorescence for the cells treated with the composition of example 1 was about 7,300. This represents a 15% increase in collagen I.

Table 2 – Collagen III

	Blank	SFM	Cells treated with composition of example 1
OD1	802	7485	10398
OD2	701	7536	10420
OD3	731	6781	10192
OD4	696	7532	9953
OD5	671	6900	10241
OD6	699	7687	9991
OD7	816	7949	10746

	Blank	SFM	Cells treated with composition of example 1
OD8	797	8122	10265
Mean OD	739.125	7499.0	10275.8
Mean OD – blank		6759.9	9536.6
SFM		163.8	89.7
P Value v control			1.47E-08
Mean OD percentage of SFM Mean OD		100%	141%

The results from Table 2 are graphed in Figure 2. The graph shows a significant difference in the collagen III levels in cells treated with serum free medium compared with cells treated with the composition of example 1. The fluorescence for the cells treated with serum free medium was about 6,800, while the fluorescence for the cells treated with the composition of example 1 was about 9,500. This represents a 41% increase in collagen III.

Example 3 – reduction in erythema

Experimental protocol:

1. The baseline assessment for each test participant was determined a day before exposure to the Solar Simulator at time = -1.

2. A Solar Simulator was used to induce mild erythema on 7 designated areas of the back of test subjects at time = 0.

3. The composition of example 1 or a control of 1% hydrocortisone cream was topically applied to the irradiated skin immediately after irradiation and again 4-5 hours later. The composition or positive control was rubbed in well upon each application. There was also a negative control involving irradiation and assessment without topical application.

4. Test subjects returned for assessment at 24 hours (t=1), 2 days (t=2), 4 days (t=3) and 7 days (t=4).

5. Assessment involved visual assessment and scoring of the erythema. In addition, colorometric measurements were taken using a Minolta Spectrophotometer Model CM-2600 and the L*a*b* colour space values recorded. The L value measures skin lightening, the a*b* values indicate change in tone against the background skin tone. Total colour change (ΔE) = $\sqrt{(\Delta L^2 + \Delta a^2 + \Delta b^2)}$. Assessments at T=1 are compared with T=2, T=3 and T=4 to quantify the improvement in colour over time.

6. Visual assessment scoring was made according to the Standard Scalar Ratings:

0 = no erythema present

1 = minimal faint (light pink), uniform or spotty erythema

2 = mild erythema, pink uniform erythema covering most of contact site

3 = moderate erythema, pink/red erythema visibly uniform in entire contact area

4 = marked bright red erythema

5 = severe deep red erythema

Results:

Table 5 - ΔE

	T=2 – T=1	T=3 – T=1	T=4 – T=1
UV only, negative control	3.0	4.4	4.6
Positive control	3.3	4.4	4.6
Composition of example 1	3.7	4.7	5.7

Table 6 – magenta to blue shift (a* at the relevant time point minus the initial a* value)

	T=2 – T=1	T=3 – T=1	T=4 – T=1
UV only, negative control	-1.7	-3.4	-3.5
Positive control	-2.3	-3.8	-3.7
Composition of example 1	-2.8	-4.1	-4.6

Table 7 – Visual assessment scoring

	T=1	T=2	T=3	T=4	% reduction
UV only, negative control	3.8	2.5	1.6	0.9	76.30
Positive control	3.7	2.7	1.7	0.9	75.70
Composition of example 1	4.1	3.1	1.8	0.8	80.50

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text. All of these different combinations constitute various alternative aspects of the invention.

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CLAIMS

1. A method of treatment or prevention of the development or recurrence of erythema in the skin of a subject comprising topical administration of a physiologically effective amount of a composition comprising disodium lauriminodipropionate tocopheryl phosphate, avena sativa kernel extract, nicotinamide, hamemalis virginiana water and menthol.

2. A method according to claim 1, wherein the subject is identified as having, being at risk of developing or being at risk of recurrence of erythema.

3. A method according to claim 1 or claim 2, wherein administration of the composition reduced the Standard Scalar Rating for the erythema by either 77% or more or 3.0 or more after 7 days.

4. A method according to any one of claims 1-3, wherein the method further comprises increasing the collagen in the skin of the subject.

5. A method according to claim 4, wherein the subject is identified as likely to benefit from increased collagen in the skin.

6. A method according to claim 4 or claim 5, wherein the increased production of collagen occurs in fibroblasts.

7. A method according to any one of claims 4-6, wherein administration of the composition increases production of collagen III by about 10% or more.

8. A method according to claim 7, wherein administration of the composition increases production of collagen III by about 40%.

9. A method according to any one of claims 4-8, wherein administration of the composition increases production of collagen I by about 5% or more.

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10. A method according to claim 9, wherein administration of the composition increases production of collagen I by about 15%.

11. A method according to any one of claims 1-10, wherein the composition further includes the vitamin panthenol.

12. A method according to any one of claims 1-11, wherein the composition is an emulsion.

13. A method according to any one of claims 1-12, wherein the composition comprises:

a. hamemalis virginiana water 0.5 to 10 percent (w/w);
b. disodium lauriminodipropionate tocopheryl phosphate in an amount equivalent to 1 to 5 percent (w/w) of a 40% active composition;
c. nicotinamide 0.5 to 5 percent (w/w);
d. avena sativa kernel extract in an amount equivalent to 0.5 to 5 percent (w/w) of a 100 ppm solution; and
e. menthol 0.01 to 0.1 percent (w/w).

14. A method according to any one of claims 1-13, wherein the composition consists essentially of:

a. disodium lauriminodipropionate tocopheryl phosphates in an amount equivalent to 1.2 percent (w/w) of a 40% active composition;
b. hamemalis virginiana water 3 percent (w/w);
c. avena sativa kernel extract in an amount equivalent to 1 percent (w/w) of a 100 ppm solution;
d. nicotinamide 1 percent (w/w);
e. menthol 0.03 percent (w/w);
f. one or more humectants, emollients, thickeners, emulsifiers, preservatives; surfactants, pH adjustors and pearling, colouring or sent agents; and
g. water q.s.

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15. A method according to any one of claims 1-14, wherein the physiologically effective amount is about 2.5mg disodium lauriminodipropionate tocopheryl phosphate applied to the face.

16. Use of a physiologically effective amount of disodium lauriminodipropionate tocopheryl phosphate in the preparation of a medicament for the topical treatment, prevention or prevention of recurrence of erythema in the skin of a subject, wherein the medicament further comprises avena sativa kernel extract, nicotinamide, hamemalis virginiana water and menthol.

17. The use according to claim 16 wherein the medicament is for increasing the collagen in the skin of the subject.

18. The use of claim 17, wherein medicament reduces the Standard Scalar Rating for the erythema by either 77% or more or 3.0 or more after 7 days.

19. The use of any one of claims 16-18, wherein the medicament increases production of collagen III by about 10% or more.

20. The use of any one of claims 16-19, wherein the medicament increases production of collagen I by about 5% or more.

21. The use of any one of claims 16-20, wherein the medicament comprises:

a. hamemalis virginiana water 0.5 to 10 percent (w/w);
b. disodium lauriminodipropionate tocopheryl phosphate in an amount equivalent to 1 to 5 percent (w/w) of a 40% active composition;
c. nicotinamide 0.5 to 5 percent (w/w);
d. avena sativa kernel extract in an amount equivalent to 0.5 to 5 percent (w/w) of a 100 ppm solution; and
e. menthol 0.01 to 0.1 percent (w/w).

Figure 1

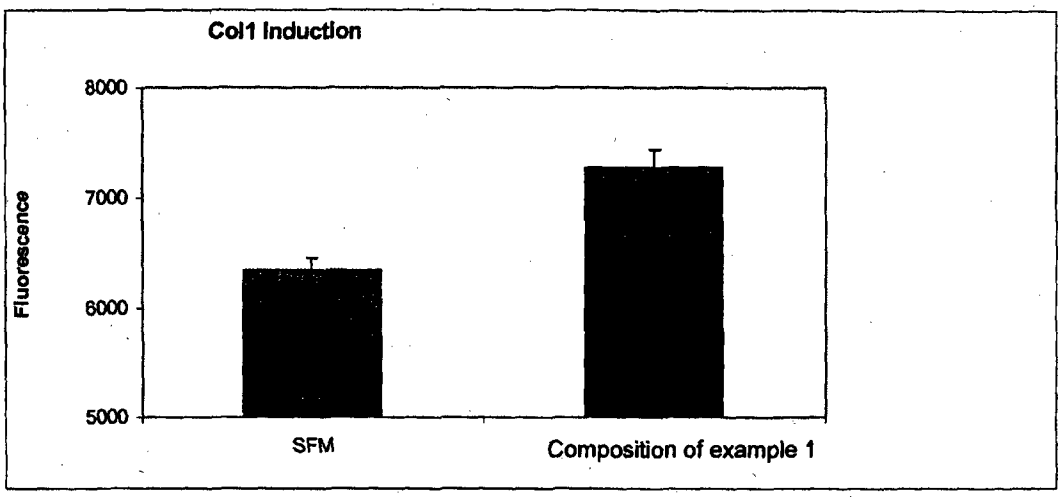

Figure 2