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(71) Applicant (for all designated States except US): **EVIDENCE SOLUÇÕES FARMACÊUTICAS LTDA EPP** [BR/BR]; Rua Padre Valdevino 1905, Aldeota, Cep: 60135-041 Fortaleza - CE (BR).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **QUEIROZ, Dinalva Brito de** [BR/BR]; Rua José Amora Sá 170 - casa 11, Coité, Cep: 61760-000 Eusébio - CE (BR).

(74) Agent: **GAIARSA, Lucas Martins**; Rua Raul Pompéia 617, Pompéia, Cep: 05025-010 São Paulo - SP (BR).

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(54) Title: A STABLE TOPICAL COMPOSITION AND A PROCESS FOR PRODUCING A STABLE TOPICAL COMPOSITION

(57) Abstract: The present invention is directed to a suitable topical composition for cosmetic, pharmaceutical or dermatological use. In a particular aspect, it is a stable nanoemulsion whose particles have a narrow size distribution range. In another particular aspect, the invention is directed to an improved process for producing said composition.



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A STABLE TOPICAL COMPOSITION AND A PROCESS FOR PRODUCING A
STABLE TOPICAL COMPOSITION

Disclosure of the Invention

The present invention is directed to a stable topical composition that is suitable for cosmetic, pharmaceutical or dermatological uses. In a particular aspect, it is directed to a stable nanoemulsion the particles of which have advantageously a narrow size distribution range. In another particular aspect, the present invention is directed to an improved process for producing said composition.

10 Background of the Invention

Topical products are being developed continuously nowadays, either to have an effect on the skin or to dispense products through the skin.

Nanoemulsions are colloidal systems that also include micelles, liposomes, virosomes, nano suspensions, micro emulsions and polymeric solutions. Nanoemulsions, based on their physical and chemical characteristics, are a sub-group of micro emulsions.

Micro emulsions are aqueous dispersions of particles composed of a lipid nucleus surrounded by monolayers of surfactants and co-surfactants.

Usually, microemulsions are produced through the mechanical fragmentation of an oleous phase in an aqueous phase in the presence of a surfactant. As is known, the very small size of oleous globules is attained by at least one passage through a high-pressure homogenizer or sonicator. It is generally known that the small size of the globules and the high homogeneity thereof distinguish microemulsions from conventional emulsions, as they are able to carry active agents more efficiently, endowing them with an increasing importance in cosmetic, medicine, and dermatology.

The present invention aims at improving a nanoemulsion-based composition. As understood herein, the

composition is nanostructured by virtue of the fact that nanoscale particles are present therein.

Description of the Invention

In a first aspect, the present invention concerns
5 a stable topical composition that comprises a specific oil-in-water nanoemulsion produced through a simple process that does not require a high-pressure homogenizer or a sonicator, wherein the oleous phase dispersed in the aqueous phase has a narrow particle size distribution, and can be modulated to
10 efficiently dispense one or more active principles incorporated in its nanoparticles, both dermally and transdermally.

Some advantages of the composition of the invention, in relation to the actives it aims at dispensing
15 dermally or transdermally, in the medicamentous area, are:

- Excellent absorption through the skin;
- High bioavailability;
- Less administrations per day;
- Absence of first pass metabolism (in the liver)
- 20 • No unpleasant flavor (by avoiding oral administration);
- Easy adaptation to change of dose;
- Easy application and consequent higher adhesion of the patient to the therapy.

Thus, the invention is about a stable topical
25 composition characterized by being composed of at least (a) a nanoemulsion that comprises at least one non-ionic emulsifying agent, at least one amphoteric surfactant, at least one emollient, at least one humectant, and at least a hydrating agent, and (b) one or more active principles
30 incorporated to the nanoemulsion oleous globules, optionally in the presence of one or more amongst oxygen-carrying agents, oleous vehicles, permeation promoters and

hydrating agents.

Without excluding any other, non-ionic emulsifying agents suitable for the invention are one or more amongst cetearyl, sorbitan and ceteareth (particularly ceteareth
5 having an ethoxylation between 6 and 20) of mixtures of fatty acid salts resulting from the saponification of vegetable oil, for example, coconut oil (cocoate), palm oil (palmate), olive oil (olivate), soy oil (soyate), sunflower seed oil, or animal oil (tallowate). Particularly one or
10 more amongst cetearyl olivate, sorbitan olivate and ceteareth-6 olivate are used.

Without excluding any other, amphoteric surfactants suitable for the invention are one or more amongst natural ones such as saponines, lecithin and soy
15 protein. Particularly, lecithin is used.

Without excluding any other, emollients suitable for the invention are one or more fatty acids among (a) those having a carbon chain between C₁₀ and C₁₈, (b) long chain polyunsaturated ones such as araquidonic,
20 eicosapentaenoic, docosahexanoic acid, as well as acids of the omega 3, omega 6 and omega 9 family, and (c) triglycerides of palmitic, oleic, linoleic, capric and caprylic acid. Particularly, use is made of a mixture of linolenic (omega 3) acid, linoleic (omega 6) acid and oleic
25 (omega 9) acid.

Without excluding any other, humectants suitable for the invention are one or more amongst polypropylene glycol, glycerin, pantenol, hialuronic acid and chondroitine sulfate. Particularly, propylene glycol is used.

30 Without excluding any other, hydrating agents that are suitable for the invention are one or more amongst disaccharides such as trehalose, maltose, and sucrose. Particularly, trehalose is used.

Without excluding any other, adequate oxygen-carrying agents are perfluorocarbon compounds, for example, perfluorotrialkylamine (preferably alkyl having 1 to 3 carbons), perfluorohexane, perfluorodimethylcyclohexane, 5 octofluorooctane and perfluorodecaline. Particularly, perfluorodecaline or a mixture of perfluorodecaline and perfluorotripropylamine is used. Within a particular embodiment of the invention, wherein an oxygen-carrying agent is used, it is contained in a liposome, for example of 10 phosphatidilcholine.

There is no specific restriction as to the active principles contained in the composition of the invention that may be dermally or transdermally dispensed, by way of topical application. Particularly, without excluding any 15 other, adequate active principles are the ones orally administered in situations where one or more of the following problems are present: the patient has difficulty in swallowing, unpleasant flavor, low bioavailability, low solubility, large chemical structures degraded into 20 undesirable metabolites, sensitivity to acidity or variation of acidity in the gastrointestinal tract, reduced concentration of the active principle through systemic metabolism (first pass effect). Particular examples of active principles are one or more amongst hormones, such as 25 estriol, estradiol, testosterone, progesterone and pregnenolone.

Optionally, the composition of the present invention contains one or more permeation promoters. Without excluding any other, suitable permeation promoters include 30 one or more among dimethyl sulfoxide, diethyleneglycol monoethyl ether, propyleneglycol dicaprilcaprate, isopropyl miristate, sodium laurylsulfate, polyoxiethylene sorbitan and sorbitan monolaurate. Particularly, diethyleneglycol

monoethyl ether is used.

Also optionally, the composition of the invention contains one or more preservative/conservation agents, to prevent microbial contamination. Without excluding other agent, preferred examples thereof include wide spectrum preservatives such as the ones that act against gram positive and gram negative bacteria, fungi and yeast. Suitable examples include one or more amongst *Lonicera japonica* extract, *Usnea barbata* extract, ferulic acid, anisic acid, tocopherol, glyceril laurate, hinokitiol (isopropyltropolone). Particularly, *Lonicera japonica* extract is used.

In an additional aspect, the invention is directed to a simple improved process for producing the above mentioned stable topical composition.

Thus, in another aspect the present invention concerns a process for producing a topical composition for dermal or transdermal administration of one or more active principles, involving the preparation of a base nanoemulsion followed by the incorporation of one or more active principles characterized by comprising the following steps:

- a. Preparing a first mixture of humectant with a portion of the total water, and heating the mixture.
- b. Preparing a second mixture containing emollient and surfactant, until solubilization, adding a non-ionic emulsifying agent, and then heating the mixture.
- c. bringing both mixtures (a) in (b) to a temperature between about 70 and 80°C, discontinuing the heating, pouring the mixture of (a) onto the mixture of (b), under constant agitation, until a homogeneous emulsion is obtained;
- d. Under agitation, removing the heating until a temperature lower than about 40°C is reached, and then

pouring onto it a pre-prepared solution of hydrating agent with the remaining of the total water; keeping under vigorous agitation, preferably for at least two hours.

5 e. If the active principle is solid, submitting same to atomization before the following step.

f. Optionally, adding to the active principle one or more of the following: a permeation promoter, an oleous vehicle, an oxidizing agent and a hydrating agent, homogenizing the mixture.

10 g. Adding the mixture of step (f) to the emulsion of step (d).

h. Grinding the emulsion obtained until completely homogenized.

i. Optionally, mixing the oxygen-carrying agent.

15 j. If necessary, adjusting the pH of the emulsion to between about 6 and 7.

Steps (a) the (d) are related to the preparation of the base nanoemulsion of the stable topical composition of the invention.

20 Preferably, the water used here is demineralized water.

Particularly, a preservative is also added to the pre-prepared aqueous solution of hydrating agent used in step (d), the pH of which is neutralized with a suitable acidifying agent, for example, a solution of 5% citric acid. Particularly, after step (d) the emulsion is left to rest for a period of a few hours, particularly between 12 and 24 hours, and then the pH is adjusted between about 7.5 and 7.8.

30 The oleous vehicle in step (f) is, for example, an odorless oil, particularly olive oil. Preferably, the homogenization in this step is mild.

In a suitable composition of the invention,

without excluding any other, adequate amounts of the components are as follows, being understood that variations of about more or less 20% are encompassed by the invention:

- non-ionic emulsifying agent - 6%
- 5 - emollient: 5%
- surfactant: 3%
- humectant: 5%
- hydrating agent: 1%
- microbicidal preservative/conservation agent: 0.5%
- 10 - acidifying agent: qs
- solubilizing water: qsp

The percentages above are of weight of the component in relation to the total weight of the ingredients used in steps (a) to (d) for the preparation of the base
15 nanoemulsion.

As to the other ingredients, the same mentioned variation above also applies:

- active principle: typically 1 through 20 %
- oxygen-carrying agent: 1%
- 20 - hydrating agent: 1%
- permeation promoter: 10%
- oleous vehicle: 5%
- base nanoemulsion: qsp 100%

The percentages of the latter ingredients are of
25 weight of the ingredient in relation to the total weight of all the ingredients of the composition.

EXAMPLE OF AN EMBODIMENT OF A STABLE TOPICAL HORMONE COMPOSITION.

In a suitable container, a PHASE A was prepared by
30 mixing 75 g of demineralized water and 5 g of propyleneglycol (humectant), and heating the mixture until between 70 and 80°C, under agitation.

In another container, a PHASE B was prepared by

adding 7 g of a commercial emollient (a mixture of 35 to 46.3% linolenic acid, 20.5 to 29% acid linoleic acid, 15.4 to 31.6% oleic acid, 2.9 to 6.7% palmitic acid, and about 1% of a mixture of capric and caprylic acids), and 3 g of
5 lecithin (amphoteric surfactant) to solubilize each other, and then 9 g of a commercial emulsifying agent containing cetearyl olivate, sorbitan olivate and ceteareth-6 olivate was added, under agitation and heating up to 70°C.

The aqueous phase A was poured onto the oleous
10 phase B, under constant agitation. The agitation was kept until a smooth homogeneous emulsion was obtained, which was then allowed to cool. Concomitantly, a PHASE C was prepared by solubilizing 1 g of trehalose (hydrating agent) in 1.5 g of demineralized water, and 0.5 g of *Lonicera japonica*
15 extract (preservative), and the pH thereof was neutralized with a sufficient amount of a 50% citric acid solution. When the emulsion (phase A + phase B) cooled down to a temperature below 40°C, phase C was added thereto, and the emulsion was homogenized for further 2 hours, under vigorous
20 agitation. It was left resting for 24 hours after what its pH was adjusted as required.

Up to this point of the process, a base nanoemulsion was prepared, which may be stored for later use.

25 In a suitable atomizer, two hormones were finely ground, 0.25 g of estriol and 0.1 g of estradiol (active principles).

To this ground matter, in a suitable container, 10 g of diethyleneglycol monoethyl ether (permeation promoter),
30 5 g of odorless oil (oleous vehicle) were added, and they were homogenized. Afterwards, the solubilized powder was transferred to a container containing 84 g of the base nanoemulsion, and it was homogenized slowly. Finally, 1 g of

liposome of perfluorodecaline (oxygen-carrying agent) was added and mixed up.

CLAIMS

1. A stable topical composition, characterized by the fact that it consists of at least (a) one nanoemulsion that comprises at least one non-ionic emulsifying agent, at least one amphoteric surfactant, at least one emollient, at least one humectant, and at least one hydrating agent, and (b) one or more active principles incorporated to the oleous globules of said nanoemulsion, optionally in the presence of one or more amongst oxygen-carrying agents, oleous vehicles, permeation promoters and hydrating agents.

2. The topical composition according to claim 1, characterized in that said emulsifying agent is one or more amongst cetearyl, sorbitan and ceteareth from mixtures of salts of fatty acids resulting from the saponification of vegetable oil, for example, coconut oil (cocoate), palm oil (palmate), olive oil (olivate), soy oil (soyate), sunflower seed oil, or animal oil (tallowate).

3. The topical composition according to claim 1, characterized in that said emulsifying agent is one or more amongst cetearyl, sorbitan and ceteareth from mixtures of salts of fatty acid resulting from the saponification of olive oil (olivate).

4. The topical composition according to claim 1, characterized in that said amphoteric surfactant is one or more amongst saponines, lecithin and soy protein.

5. The topical composition according to claim 1, characterized in that said amphoteric surfactant is lecithin.

6. The topical composition according to claim 1, characterized in that said emollient comprises one or more fatty acids chosen among those (a) having a carbonic chain between C10 and C18, (b) long-chain polyunsaturated ones, particularly araquidonic, eicosapentaenoic, docosahexanoic,

and linolenic (omega 3) acid, linoleic (omega 6) acid, and oleic (omega 9) acid, and (c) triglycerides of palmitic, oleic, linoleic, capric and caprylic acids.

7. The topical composition according to claim 1,
5 characterized in that said emollient is mostly a mixture of linolenic acid, linoleic acid, and oleic.

8. The topical composition according to claim 1,
characterized in that said humectant is one or more amongst polypropylene glycol, glycerin, pantenol, hialuronic acid,
10 and condroitine sulphate.

9. The topical composition according to claim 1,
characterized in that said humectant is propylene glycol.

10. The topical composition according to claim 1,
characterized in that said hydrating agent is one or more
15 amongst disaccharides, particularly trehalose, maltose and sucrose.

11. The topical composition according to claim 1,
characterized in that said hydrating agent is trehalose.

12. The topical composition according to claim 1,
20 characterized in that said oxygen-carrying agents are one or more perfluorocarbons chosen amongst perfluorotrialkylamines, particularly 1 to 3 carbon alkyl, perfluorohexane, perfluorodimethylcyclohexane, octofluorooctane and perfluorodecalin.

25 13. The topical composition according to claim 1,
characterized in that said oxygen-carrying agent is one or more amongst perfluorodecaline and a mixture of perfluorodecaline and perfluorotripropilamine.

14. The topical composition according to claim 1,
30 characterized in that said carrier it is contained in a liposome, particularly a phosphatidilcholine liposome.

15. The topical composition according to claim 1,
characterized in that said active principle is chosen

amongst those having one or more restrictions in order to be delivered orally, such as: patient with difficulty in swallowing, unpleasant flavor, low bioavailability, low solubility, chemical structure subject to the undesirable formation of metabolites, reduction of the concentration by the pre-systemic metabolism (first pass metabolism), and sensitivity to acidity or variation of the acidity in the gastrointestinal tract.

16. The topical composition according to claim 1, characterized in that said active principle is one or more hormones amongst estriol, estradiol, testosterone, progesterone and pregnenolone.

17. The topical composition according to claim 1, characterized in that said permeation promoter is one or more amongst dimethyl sulfoxide, diethylene glycol monoethyl ether, propylene glycol dicaprilcaprate, isopropyl miristate, sorbitan sodium lauryl sulfate, polyoxiethylene monooleate, and sorbitan monolaurate.

18. The topical composition according to claim 1, characterized in that said permeation promoter is diethyleneglycol monoethyl ether.

19. The topical composition according to claim 1, characterized in that said preservative agent is one or more amongst *Lonicera japonica* extract, *Usnea barbata* extract, ferulic acid, anisic acid, tocopherol, glyceril laurate, isopropyltropolone.

20. The topical composition according to claim 1, characterized in that said preservative agent is an extract of *Lonicera japonica*.

21. A process for producing a topical composition according to claim 1, characterized by comprising the following steps:

a. preparing a first mixture of humectant with a part of

the total water, and heating the mixture;

b. preparing a second mixture containing emollient and surfactant, until solubilization, adding a non-ionic emulsifying agent, and then heating the mixture;

5 c. bringing both mixtures (a) in (b) to a temperature between about 70 and 80°C, discontinuing the heating, pouring the mixture of (a) onto the mixture of (b), under constant agitation, until a homogeneous emulsion is obtained;

10 d. under agitation, removing the heating until a temperature lower than about 40°C is reached and then pouring onto it a pre-prepared solution of hydrating agent with the remaining of the total water; keeping under vigorous agitation, preferably during at least two hours;

15 e. if the active principle is solid, submitting same to atomization before the next step;

f. optionally, adding to the active principle one or more amongst the following: a permeation promoter, an oleous vehicle, an oxidizing agent and hydrating agent,

20 homogenizing the mixture;

g. adding the mixture of step (f) to the emulsion of step (d);

h. grinding the final emulsion until it is completely homogenized;

25 i. optionally, mixing the oxygen-carrying compound;

j. if necessary, adjusting the pH of the emulsion to between about 6 and 7.

22. The process for producing a topical composition according to claim 2, characterized in that, to
30 the pre-prepared solution of hydrating agent with water, in step (d), previously neutralized preservative/conservation microbicide, particularly *Lonicera japonica* extract, is added

23. The process for producing a topical composition according to claim 21, characterized in that, after the step (d) the final emulsion is left resting for a period of a few hours, particularly between 12 and 24 hours, and then its pH is adjusted, particularly to between 7.5 and 7.8.

24. The process according to claim 21, characterized in that the amounts of the components used between the steps (a) e (d), for obtaining a base nanoemulsion, are as follows, including variations of about more or less 20%, in percentages by weight: 6% non-ionic emulsifying agent, 5% emollient, 3% surfactant, 5% humectant, 1% hydrating agent, 0.5% preservative/conservation microbicide, an amount of acidifying agent enough to adjust the pH, and an amount of water enough to complete 100%.

25. The process according to claim 21, characterized in that the amounts of the components utilized between the steps (e) e (j) for completing said process are as follows, including variations of about more or less 20%, in percentages by weight: 1 to 20% active principle, 1% oxygen-carrying agent, 1% hydrating agent, 10% permeation promoter, 5% oleous vehicle 5% and an amount of nanoemulsion base to complete 100%.

26. The process according to claim 21, characterized in that a nanoemulsion base resulting from the steps (a) to (d) can be stored for later use in performing the other steps of said process.