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(54) **GEL COMPOSITION FOR ONCE-DAILY TREATMENT OF COMMON ACNE COMPRISING A COMBINATION OF BENZOYL PEROXIDE AND ADAPALENE AND/OR ADAPALENE SALT**

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See application file for complete search history.

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(57) **ABSTRACT**

Dermatological/cosmetic gel compositions suited for preventing or treating cell differentiation and/or proliferation and/or keratinization disorders, including preventing or treating common acne, comprise (i) at least one retinoid, (ii) dispersed benzoyl peroxide and (iii) at least one pH-independent gelling agent, formulated into (iv) a physiologically acceptable medium therefor.

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GEL COMPOSITION FOR ONCE-DAILY TREATMENT OF COMMON ACNE COMPRISING A COMBINATION OF BENZOYL PEROXIDE AND ADAPALENE AND/OR ADAPALENE SALT

CROSS-REFERENCE TO PRIORITY/PROVISIONAL APPLICATIONS

This application claims priority under 35 U.S.C. §119 of FR-01/16747, filed Dec. 21, 2001, and of provisional application Ser. No. 60/351,382, filed Jan. 28, 2002, both hereby expressly incorporated by reference. This application is also a continuation of said '382 provisional.

BACKGROUND OF THE INVENTION

1. Technical Field of the Invention

The invention relates to a composition comprising, in a physiologically acceptable medium, at least one retinoid, dispersed benzoyl peroxide and at least one pH-independent gelling agent.

2. Description of the Prior Art

The use of several classes of active principles is a therapeutic tool that is frequently employed, especially for treating dermatological disorders.

Specifically, it is known practice in the treatment of dermatitis to use corticosteroids such as, for example, hydrocortisone, miconazole or betamethasone valerate, antihistamines (e.g., mizolastine) and/or keratolytic agents, for instance salicylic acid. Various antifungal agents, for instance allylamine derivatives, triazoles, antibacterial agents or antimicrobial agents such as, for example, antibiotics, quinolones and imidazoles, are also conventionally combined in the treatment of dermatological diseases. Peroxides, D vitamins and retinoids are also described for the topical treatment of various pathologies associated with the skin or mucous membranes, in particular acne.

The combination of several local treatments (antibiotics, retinoids, peroxides and zinc) is also used in dermatology to increase the efficacy of the active principles and to reduce their toxicity (Cunliffe W. J., *J. Dermatol. Treat.,* 2000, 11 (suppl2), pp. 13-14).

The multiple application of various dermatological products may be relatively burdensome and restricting for the patient.

The value in seeking to obtain a novel treatment that is effective on dermatological complaints in a stable composition offering good cosmetic utility, allowing a single application and a utilization that the patient finds pleasant, may thus be appreciated.

Among this panoply of treatments proposed to a person skilled in the art, there was nothing to encourage him to combine, in the same composition, benzoyl peroxide and a retinoid.

However, formulating such a composition poses several problems.

Firstly, the efficacy of benzoyl peroxide is associated with its decomposition when it is placed in contact with the skin. Specifically, it is the oxidizing properties of the free radicals produced during this decomposition that lead to the desired effect. Thus, in order to maintain the optimum efficacy of benzoyl peroxide, it is important to prevent its decomposition before use, i.e., during storage.

The solubility and stability of benzoyl peroxide were studied by Chellquist et al., in ethanol, propylene glycol and various mixtures of polyethylene glycol 400 (PEG 400) and water (Chellquist E. M. and Gorman W. G., *Pharm. Res.,* 1992, Vol 9: 1341-1346). Benzoyl peroxide is particularly soluble in PEG 400 and ethanol, as shown in the following table:

Solvent	Benzoyl peroxide solubility (mg/g)
PEG 400	39.6
Ethanol	17.9
Propylene glycol	2.95
Propylene glycol/water (75:25)	0.36
Glycerol	0.15
Water	0.000155

The said document moreover states that the stability of benzoyl peroxide is greatly influenced by the chemical composition of the formulation and by storage temperature. Benzoyl peroxide is extremely reactive and degrades in solution at low temperature on account of the instability of its peroxide bond. The authors thus state that benzoyl peroxide in solution degrades more or less quickly in all the solvents studied as a function of the type of solvent and of its concentration.

The degradation times for benzoyl peroxide in PEG 400 (0.5 mg/g), in ethanol and in propylene glycol are, respectively, 1.4, 29 and 53 days at 40° C.

Such a degradation does not allow the preparation of a product intended for sale.

It is moreover known that benzoyl peroxide is more stable in water and propylene glycol when it is in suspension (i.e., in dispersed form), since it is not degraded after storage for 90 days in these solvents. Thus, in order to limit the problem of rapid instability of benzoyl peroxide in solution, it has been found to be advantageous to formulate benzoyl peroxide in dispersed form. However, this type of formulation is not entirely satisfactory since degradation of the benzoyl peroxide in the finished product is still observed.

Another difficulty to be overcome in preparation of a composition comprising both benzoyl peroxide and a retinoid is that most retinoids are particularly sensitive to natural oxidation, to visible light and to ultraviolet light, and, since benzoyl peroxide is a strong oxidizing agent, the chemical compatibility of these compounds in the same formulation poses numerous problems in terms of physical and chemical stability.

A study of the stability of two retinoids was performed by combining two commercial products, one containing a retinoid (tretinoin or adapalene) and the second based on benzoyl peroxide (B. Martin et al., *Br. J. Dermatol.* (1998) 139, (suppl. 52), 8-11). The presence of the formulation based on benzoyl peroxide results in very rapid degradation of the oxidation-sensitive retinoids: it is measured that 50% of the tretinoin is degraded in 2 hours, and 95% in 24 hours. In the composition in which the retinoid is adapalene, no degradation of the adapalene was measured over 24 hours. This study confirms that benzoyl peroxide becomes degraded and degrades oxidation-sensitive retinoids over time, gradually releasing benzoic acid into the finished products. In contrast, no indication is given regarding the physical stability of the two compositions placed in contact, or regarding the therapeutic activity that may finally be obtained by combining the two active

a stable composition of gel type, given that it was commonly known that the presence of benzoyl peroxide chemically and physically destabilized this type of composition.

Now, it is clear that the degradation of benzoyl peroxide and retinoids is not desirable since it impairs the efficacy of the composition containing them.

Moreover, a finished product, in particular when it is a pharmaceutical or cosmetic composition, must maintain throughout its shelf life precise physicochemical criteria for ensuring its pharmaceutical or cosmetic quality, respectively. Among these criteria, it is necessary for the rheological properties to be maintained. They define the behavior and texture of the composition during application, but also the active principle's release properties [1998 SFSTP Commission Report] and the homogeneity of the product when the active principles are present therein in dispersed form.

In particular, the formulation of benzoyl peroxide and of a retinoid in gel form is advantageous for topical treatments, such as the treatment of acne, since it especially avoids a greasy feel being left on the skin.

Another difficulty to be overcome in preparing a composition especially comprising benzoyl peroxide, when it is in gel form, is that the gelling agents are destabilized by the benzoic acid released during the degradation of the benzoyl peroxide.

Specifically, the thickeners most commonly used for formulating these compositions with benzoyl peroxide are acrylic acid polymers (Carbomer) and celluloses alone or combined with silicates.

Now, the use of carbomers in compositions of aqueous gel type does not give good results in terms of chemical stability of the benzoyl peroxide or in terms of rheological stability. As described by Bollinger (Bollinger, Journal of Pharmaceutical Science, 1977, vol 5), it has been observed that from 5% to 20% benzoyl peroxide is lost after 2 months at 40° C. depending on the neutralizer of the carbomer used. Furthermore, the release of benzoic acid results in depolymerization of the carbomers, leading to a drop in viscosity which may result in phase separation. In other gels consisting of a mixture of hydroxypropyl-cellulose and aluminum magnesium silicate, a drop in viscosity over time is also observed, resulting in sedimentation of the active agents as a suspension and heterogeneity of the dispersion in the finished product.

This instability of benzoyl peroxide gels impairs their efficacy and their cosmetic utility.

There is thus still a need for a physically stable gelled composition containing benzoyl peroxide and a retinoin.

SUMMARY OF THE INVENTION

The Applicant has now, surprisingly, produced a composition that satisfies this need, which comprises dispersed, free or encapsulated benzoyl peroxide, at least one retinoid and a pH-independent gelling agent with good physical stability, i.e., not showing a drop in viscosity over time and at temperatures of between 4 and 40° C., and maintaining good chemical stability of the two active agents (benzoyl peroxide and retinoid), i.e., no degradation of the active agents over time and at temperature of between 4 and 40° C. is observed. The Applicant has also discovered, surprisingly, that total dispersion of the active principles can be obtained by following a particular preparation process. This preparation process performed without heat makes it possible to obtain an optimum particle size and uniform dispersion of the two active agents

The invention thus relates to a composition comprising, in a physiologically acceptable medium, at least one retinoid, dispersed benzoyl peroxide and at least one pH-independent gelling agent.

DETAILED DESCRIPTION OF BEST MODE AND SPECIFIC/PREFERRED EMBODIMENTS OF THE INVENTION

The composition according to the invention is preferably in the form of an aqueous gel.

The term "aqueous gel" means a composition containing, in an aqueous phase, a viscoelastic mass formed from colloidal suspensions (gelling agent).

The expression "pH-independent gelling agent" means a gelling agent capable of giving the composition a viscosity that is sufficient to keep the retinoid and the benzoyl peroxide in suspension, even under the influence of a variation in pH caused by the release of benzoic acid by the benzoyl peroxide.

Non-limiting examples that may be mentioned include the gelling agents of the polyacrylamide family, such as the mixture of sodium acryloyldimethyltaurate copolymer/isohexadecane/polysorbate 80 sold under the name Simulgel 600 by the company SEPPIC, the mixture of polyacrylamide/isoparaffin C13-14/laureth-7 such as, for example, the product sold under the name Sepigel 305 by the company SEPPIC, the family of acrylic polymers coupled to hydrophobic chains, such as the PEG-150/decyl/SMDI copolymer sold under the name Aculyn 44 (polycondensate comprising at least, as components, a polyethylene glycol containing 150 or 180 mol of ethylene oxide, decyl alcohol and methylenebis (4-cyclohexyl isocyanate) (SMDI), at 35% by weight in a mixture of propylene glycol (39%) and water (26%)), the family of modified starches, such as the modified potato starch sold under the name Structure Solanace, or mixtures thereof.

The preferred gelling agents are derived from the polyacrylamide family, such as Simulgel 600 or Sepigel 305, or mixtures thereof.

The gelling agent as described above may be used in preferential concentrations ranging from 0.1% to 15% and more preferably ranging from 0.5% to 5%.

The composition according to the invention contains at least one retinoid.

The term "retinoid" means any compound that binds to the RAR and/or RXR receptors.

Preferably, the retinoid is a compound chosen from the family of benzonaphthalene retinoids as described in patent application EP 0 199 636. In particular, adapalene and also precursors and/or derivatives thereof will be preferred.

The expression "retinoid precursors" means the immediate biological precursors or substrates thereof, and also the chemical precursors thereof.

The expression "retinoid derivative" means both their metabolic derivatives and their chemical derivatives.

Other retinoids may be chosen from those described in the following patents or patent applications: U.S. Pat. No. 4,666,941, U.S. Pat. No. 4,581,380, EP 0 210 929, 15 EP 0 232 199, EP 0 260 162, EP 0 292 348, EP 0 325 540, EP 0 359 621, EP 0 409 728, EP 0 409 740, EP 0 552 282, EP 0 584 191, EP 0 514 264, EP 0 514 269, EP 0 661 260, EP 0 661 258, EP 0 658 553, EP 0 679 628, EP 0 679 631, EP 0 679 630, EP 0 708 100, EP 0 709 382, EP 0 722 928, EP 0 728 739, EP 0 732 328, EP 0 740 937, EP 0 776 885, EP 0 776 881, EP 0 823 903, EP 0 832 057, EP 0 832 081, EP 0 816 352, EP 0 826 657, EP 0 874 626, EP 0 934 295, EP 0 915 823, EP 0 882 033, EP 0 850 909,

Needless to say, the amount of the two active agents, benzoyl peroxide and retinoid, in the composition according to the invention will depend on the combination chosen and thus particularly on the retinoid under consideration and the quality of the desired treatment.

The preferred retinoid concentrations are between 0.0001% and 20% by weight relative to the total weight of the composition.

Benzoyl peroxide may also be used in free form or in an encapsulated form in a form adsorbed onto, or absorbed in, any porous support. It may be, for example, benzoyl peroxide encapsulated in a polymer system consisting of porous microspheres, such as, for example, microsponges sold under the name Microsponges P009A Benzoyl peroxide by the company Advanced Polymer System.

To give an order of magnitude, the composition according to the invention advantageously comprises between 0.0001% and 20% by weight of benzoyl peroxide and between 0.0001% and 20% by weight of retinoid relative to the total weight of the composition, and preferably, respectively, between 0.025% and 10% by weight of benzoyl peroxide and between 0.001% and 10% by weight of retinoid relative to the total weight of the composition.

For example, in compositions for treating acne, the benzoyl peroxide is preferably used at concentrations ranging from 2% to 10% by weight and more particularly from 2.5% to 5% by weight, relative to the total weight of the composition. As regards the retinoid, it is used in this type of composition at concentrations generally ranging from 0.05% to 1% by weight relative to the total weight of the composition.

Advantageously, the particle size of the retinoid and of the benzoyl peroxide is such that at least 80% in numerical terms of the particles, and preferably at least 90% in numerical terms of the particles, have a diameter of less than 25 μm and at least 99% in numerical terms of the particles have a diameter of less than 100 μm.

According to the invention, the gel containing benzoyl peroxide and a retinoid advantageously comprises at least water and may also comprise a pro-penetrating agent and/or a liquid wetting surfactant.

The compositions of the invention may contain one or more pro-penetrating agents in preferential concentrations ranging from 0% to 20% and more preferably ranging from 2% to 6% by weight, relative to the total weight of the composition. They should generally not dissolve the active agents at the percentage used, should not cause any exothermic reactions harmful to the benzoyl peroxide, should aid in the satisfactory dispersion of the active agents, and should have antifoaming properties. Among the pro-penetrating agents preferably used, without this list being limiting, are compounds such as propylene glycol, dipropylene glycol, propylene glycol dipelargonate, lauroglycol and ethoxydiglycol.

The pro-penetrating agent that is particularly preferred is propylene glycol.

Advantageously, the compositions according to the invention may also contain one or more liquid wetting surfactants in preferential concentrations ranging from 0% to 10% and more preferably ranging from 0.1% to 2%. The wetting power is the tendency of a liquid to spread over a surface.

They are preferably surfactants with an HLB (Hydrophilic-Lipophilic Balance) value from 7 to 9, or nonionic surfactants such as polyoxyethylenated and/or polyoxypropylenated copolymers. They should be liquid so as to be readily incor-

Among the wetting agents that are preferably used, without this list being limiting, are compounds of the Poloxamer family and more particularly Poloxamer 124 and/or Poloxamer 182.

The liquid wetting surfactant that is particularly preferred is Poloxamer 124.

The composition may also comprise any additive usually used in the cosmetics or pharmaceutical field, such as sequestering agents, antioxidants, sunscreens, preserving agents, fillers, electrolytes, humectants, colorants, common mineral or organic acids or bases, fragrances, essential oils, cosmetic active agents, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds such as DHA, and calmants and protective agents for the skin such as allantoin. Needless to say, a person skilled in the art will take care to select this or these optional additional compound(s), and/or the amount thereof, such that the advantageous properties of the composition according to the invention are not, or are not substantially, adversely affected.

These additives may be present in the composition in a proportion of from 0% to 20% by weight relative to the total weight of the composition.

Examples of sequestering agents that may be mentioned include ethylenediaminetetraacetic acid (EDTA), and also derivatives or salts thereof, dihydroxyethylglycine, citric acid and tartaric acid, or mixtures thereof.

Examples of preserving agents that may be mentioned include benzalkonium chloride, phenoxy-ethanol, benzyl alcohol, diazolidinylurea and parabens, or mixtures thereof.

Examples of humectants that may be mentioned include glycerol and sorbitol.

In particular, the invention also relates to a pharmaceutical or cosmetic composition for topical application to the skin, the integuments or mucous membranes, in the form of an aqueous gel, characterized in that it contains, in a physiologically acceptable medium that is compatible with topical application to the skin, the integuments or mucous membranes, an active phase comprising (expressed in percentages by weight):

0% to 90%, preferably 5% to 25% and especially 10% to 20%, of water;

0% to 10%, preferably 0 to 2% and especially 0% to 0.5%, of liquid wetting surfactant;

0% to 20%, preferably 0% to 10% and especially 2% to 5%, of pro-penetrating agent;

0.0001% to 20% and preferably 0.025% to 10%, of benzoyl peroxide;

0.0001% to 20% and preferably 0.001% to 10%, of retinoid; and

an aqueous phase comprising a pH-independent gelling agent, and water.

The aqueous phase of the emulsion according to the invention may comprise water, a floral water such as cornflower water, or natural mineral or spring water chosen, for example, from eau de Vittel, waters of the Vichy basin, eau d'Uriage, eau de la Roche Posay, eau de la Bourboule, eau d'Enghien-les-Bains, eau de Saint Gervais-les-Bains, eau de Néris-les-Bains, eau d'Allevard-les-Bains, eau de Digne, eau de Maizières, eau de Neyrac-les-Bains, eau de Lons-le-Saunier, les Eaux Bonnes, eau de Rochefort, eau de Saint Christau, eau des Fumades, eau de Tercis-les-bains, eau d'Avène or eau d'Aix les Bains.

The said aqueous phase may be present in a content of between 10% and 90% by weight and preferably between

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