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(54) **PHARMACEUTICAL/COSMETIC, E.G., ANTI-ACNE COMPOSITIONS COMPRISING AT LEAST ONE NAPHTHOIC ACID COMPOUND, BENZOYL PEROXIDE AND AT LEAST ONE FILM-FORMING AGENT**

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(57) **ABSTRACT**

Stable pharmaceutical/cosmetic compositions for topical application, notably for the treatment of acne vulgaris include, formulated into a physiologically acceptable medium, at least one naphthoic acid compound, benzoyl peroxide and at least one film-forming agent, the at least one naphthoic acid compound and the benzoyl peroxide advantageously being in a dispersed form therein.

PHARMACEUTICAL/COSMETIC, E.G., ANTI-ACNE COMPOSITIONS COMPRISING AT LEAST ONE NAPHTHOIC ACID COMPOUND, BENZOYL PEROXIDE AND AT LEAST ONE FILM-FORMING AGENT

CROSS-REFERENCE TO PRIORITY APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §120 of U.S. Provisional Application No. 61/004,763, filed Nov. 30, 2007 and is a continuation of PCT/FR 2008/052169, filed Dec. 1, 2008 and designating the United States (published in the French language on Jun. 25, 2009 as WO 2009/077693 A2; the title and abstract were also published in English), each hereby expressly incorporated by reference in its entirety and each assigned to the assignee hereof.

BACKGROUND OF THE INVENTION

[0002] 1. Technical Field of the Invention

[0003] The present invention relates to compositions for topical application, to processes for preparing such compositions and to applications thereof as cosmetic or pharmaceutical products, the compositions being particularly useful for treating acne.

[0004] 2. Description of Background and/or Related and/or Prior Art

[0005] Acne is a common multi-factor pathology that attacks skin rich in sebaceous glands (face, shoulder area, arms and intertriginous areas). It is the most commonly occurring form of dermatosis. The following five pathogenic factors play a determining role in the development of acne:

[0006] 1. genetic predisposition;

[0007] 2. overproduction of sebum (seborrhoea);

[0008] 3. androgens;

[0009] 4. follicular keratinization disorders (comedogenesis); and

[0010] 5. bacterial colonization and inflammatory factors.

[0011] There are several forms of acne, the common factor of all of them being attack of the pilosebaceous follicles. Exemplary are acne conglobata, acne keloid on the nape of the neck, acne medicamentosa, recurrent miliary acne, acne necrotica, acne neonatorum, premenstrual acne, occupational acne, acne rosacea, senile acne, solar acne and acne vulgaris.

[0012] Acne vulgaris, also known as polymorphous juvenile acne, is the most common. It comprises four stages, but it is not necessary to pass through all the stages:

[0013] Stage 1 corresponds to comedonal acne, characterized by a large number of open and/or closed comedones and of microcysts.

[0014] Stage 2, or papulopustular acne, is of mild to moderate seriousness. It is characterized by the presence of open and/or closed comedones and microcysts, but also of red papules and of pustules. It mainly affects the face and leaves few scars.

[0015] Stage 3, or papulocomedonal acne, is more serious and extends to the back, the thorax and the shoulders. It is accompanied by a larger number of scars.

[0016] Stage 4, or nodulocystic acne, is accompanied by numerous scars. It exhibits nodules and also has large painful purplish pustules.

[0017] The various forms of acne described above can be treated with active agents, such as antiseborrhoeics and antiinfectives, for example benzoyl peroxide (in particular, the product Eclaran® marketed by Pierre Fabre), with retinoids, such as tretinoin (in particular, the product Retacnyl® marketed by Galderma) or isotretinoin (the product Roaccutane® marketed by Laboratoires Roche), or with naphthoic acid compounds. Naphthoic acid compounds, such as, in particular, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, commonly known as adapalene (the product Differine® marketed by Galderma), are widely described and recognized as active ingredients which are as effective as tretinoin in the treatment of acne.

[0018] The combination of several local treatments (antibiotics, retinoids, peroxides, zinc) is also used in dermatology to increase the efficacy of the active ingredients and to reduce their toxicity (Cunliffe W. J., J. Dermatol. Treat., 2000, 11 (suppl. 2), S13-S14) but the multiple application of various dermatological products can be quite laborious and demanding for the patient.

[0019] The advantage of providing a new treatment which is effective under dermatological conditions, in a stable composition offering good cosmeticity, and which can be applied just once and is pleasant for the patient to use, is therefore apparent.

[0020] Among this panoply of therapeutics proposed to those skilled in the art, none would encourage one to combine, in the same composition, benzoyl peroxide and a retinoid.

[0021] However, the formulation of such a composition presents several problems.

[0022] First, the efficacy of benzoyl peroxide is linked to its decomposition when it is brought into contact with the skin. In fact, it is the oxidizing properties of the free radicals produced during this decomposition which result in the desired effect. Thus, to maintain optimum efficacy of the benzoyl peroxide, it is important to prevent it from decomposing before use, i.e., during storage.

[0023] However, benzoyl peroxide is an unstable chemical compound, which makes it difficult to formulate it into final products.

[0024] The solubility and stability of benzoyl peroxide have been 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).

[0025] This prior art specifies, moreover, that the stability of benzoyl peroxide is greatly influenced by the chemical composition of the formulation and by the storage temperature thereof. Benzoyl peroxide is extremely reactive and degrades in solution at low temperature due to the instability of its peroxide bond.

[0026] The authors thus note that benzoyl peroxide in solution degrades more or less rapidly in all of the solvents studied, depending on the type of solvent and on the concentration thereof.

[0027] The degradation times of 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.

[0028] Such a degradation does not make it possible to formulate a product intended for sale.

[0029] Another difficulty to be overcome in the formulation 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 radiation, and since benzoyl peroxide is a strong oxidizing agent, the chemical compatibility of these compounds in the same for-

mulation poses numerous problems of stability from the physical and chemical point of view.

[0030] A study of the stability of two retinoids was carried out by combining two commercially available products, one containing a retinoid (tretinoin or adapalene) and the second being benzoyl peroxide-based (B. Martin et al., *Br. J. Dermatol.* (1998) 139 (suppl. 52), 8-11).

[0031] The presence of the benzoyl peroxide-based formulation causes very rapid degradation of the oxidation-sensitive retinoids: it is measured that 50% of the tretinoin degrades in 2 hours, and 95% in 24 hours. In the composition in which the retinoid is adapalene, no degradation of the adapalene was measured for 24 hours. This study confirms that benzoyl peroxide is degraded and degrades oxidation-sensitive retinoids over time, gradually releasing benzoic acid into final products.

[0032] However, it is apparent that the degradation of benzoyl peroxide and of retinoids is undesirable since it is detrimental to the effectiveness of the composition containing them.

[0033] Nothing would prompt the combination of these two active agents to obtain a stable composition, given that it was customarily known that the presence of benzoyl peroxide chemically and physically destabilized this type of composition.

[0034] Furthermore, those skilled in the art are constantly seeking to improve the efficacy and tolerance of compositions containing benzoyl peroxide and a naphthoic acid compound. One of the solutions for improving the efficacy is to increase the amounts of active agents present in the composition or to increase the treatment times. Such modifications generally result in an increase in the induced irritation. For this reason, it is necessary to provide compositions that can further improve the tolerance of the active ingredients.

SUMMARY OF THE INVENTION

[0035] The present invention provides compositions that are stable and less irritant than those of the prior art. Such compositions furthermore promote the topical penetration of the active ingredients in dispersed form.

[0036] Thus, it has now surprisingly, been demonstrated that ingredients that are known for providing a composition a film-forming effect may also improve the tolerance of the combination of two irritant active ingredients, such as anti-acne active ingredients, and in particular benzoyl peroxide and naphthoic acid compounds, such as adapalene.

[0037] Thus, the present invention provides compositions for topical application that are particularly effective, comprising at least one naphthoic acid compound and benzoyl peroxide, devoid of an obviously irritant effect that would prevent same from being used over a relatively long term by the individual.

[0038] This invention thus features compositions for topical application, comprising, in a physiologically acceptable medium, at least one naphthoic acid compound and benzoyl peroxide and at least one film-forming agent, said naphthoic acid compound being in a dispersed form in said composition.

[0039] Thus, the present invention features compositions, preferably pharmaceutical compositions, in particular for topical application, comprising, formulated into a physiologically acceptable medium, at least:

[0040] (i) one naphthoic acid compound,

[0041] (ii) benzoyl peroxide, and

[0042] (iii) a film-forming agent,

said naphthoic acid compound and said benzoyl peroxide being in a dispersed form in said composition.

[0043] According to the invention, the term "active agent in dispersed form" means an active ingredient in the form of solid particles, suspended in a given carrier. Such particles are in particular greater than 10 μm in size.

[0044] Advantageously, the particle size of the retinoid and of the benzoyl peroxide is such that at least 80% by number of the particles, and preferably at least 90% by number of the particles, have a diameter of less than 25 μm, and at least 99% by number of the particles have a diameter of less than 100 μm.

[0045] The present invention also features a process for formulating a composition for topical application, comprising the step of mixing a physiologically acceptable carrier including at least one naphthoic acid derivative and benzoyl peroxide with at least one film-forming agent, said naphthoic acid compound and the benzoyl peroxide being in a dispersed form in said composition. The term "physiologically acceptable carrier" means a carrier compatible with the skin, the mucous membranes and/or the integuments.

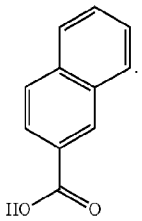
[0046] Finally, this invention also features the formulation of a composition as described above, into medicaments useful for the treatment and/or prevention of dermatological conditions/afflictions associated with a keratinization disorder relating to cell differentiation and proliferation, and in particular for preventing and/or treating comedonal acne, acne vulgaris, papulocomedonal acne, nodulocystic acne, polymorphic acne, acne rosacea, acne conglobata, senile acne, or else secondary acne such as solar acne, acne medicamentosa or occupational acne.

[0047] When a composition comprises, in a physiologically acceptable medium, at least one naphthoic acid compound, benzoyl peroxide and at least one film-forming agent, said naphthoic acid compound and the benzoyl peroxide being in a dispersed form in said composition, it shows very good tolerance without modifying the amount of active agent that has penetrated into the skin.

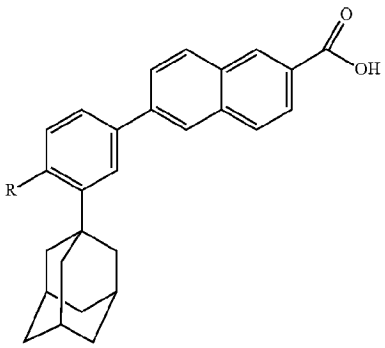
DETAILED DESCRIPTION OF BEST MODE AND SPECIFIC/PREFERRED EMBODIMENTS OF THE INVENTION

[0048] The compositions according to the invention comprise at least one naphthoic acid compound, benzoyl peroxide and at least one film-forming agent.

[0049] Naphthoic acid is a compound having the formula:



[0050] The term "naphthoic acid compound" means those compounds of formula (I):



(I)

in which R is a hydrogen atom, a hydroxyl radical, a branched or unbranched alkyl radical having from 1 to 4 carbon atoms, an alkoxy radical having from 1 to 10 carbon atoms or a substituted or unsubstituted cycloaliphatic radical.

[0051] The term "linear or branched alkyl radical having from 1 to 4 carbon atoms" means, preferably, methyl, ethyl, propyl and butyl radicals.

[0052] The term "alkoxy radical having from 1 to 10 carbon atoms" means, preferably, methoxy, ethoxy, propoxy, butoxy, hexyloxy and decyloxy radicals.

[0053] The term "cycloaliphatic radical" means, preferably, monocyclic or polycyclic radicals such as the 1-methylcyclohexyl radical or the 1-adamantyl radical.

[0054] Among the naphthoic acid compounds that may be formulated into the compositions according to the invention, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (adapalene), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid, 6-[3-(1-adamantyl)-4-decyloxyphenyl]-2-naphthoic acid and 6-[3-(1-adamantyl)-4-hexyloxyphenyl]-2-naphthoic acid will advantageously be selected.

[0055] The abovementioned naphthoic acid compounds are generally in a dispersed form in the composition according to the invention. The insoluble naphthoic acid compounds are thus uniformly distributed in the compositions according to the invention.

[0056] In the compositions according to the invention, the naphthoic acid compounds are used at concentrations of less than or equal to 10% by weight relative to the total weight of the composition, and are preferably from 0.001% to 10% by weight relative to the total weight of the composition, and preferentially from 0.01% to 5%, more preferentially from 0.05% to 2%, and most preferentially from 0.1% to 0.3% by weight relative to the total weight of the composition.

[0057] Throughout the present text, unless otherwise specified, it is understood that, when concentration ranges are given, they include the upper and lower limits of said range.

[0058] Advantageously, the naphthoic acid compound in the compositions according to the invention is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (adapalene). Preferably, in the case of adapalene, the compositions according to the invention comprise from 0.001% to 5%, and advantageously from 0.01% to 1% by weight of adapalene, relative to the total weight of the composition, preferentially from 0.01% to 0.5%, preferably from 0.1% to 0.4% by weight of adapalene, more preferentially still at 0.1% or at 0.3% by weight of adapalene.

[0059] The subject compositions also comprise benzoyl peroxide (BPO).

[0060] In the compositions according to the invention, the benzoyl peroxide is included at concentrations ranging from 1% to 10% by weight, more particularly from 2% to 7% by weight, more preferentially still from 2.5% to 5% by weight, relative to the total weight of the composition.

[0061] The benzoyl peroxide may equally be in the free form or else in an encapsulated form in a form adsorbed onto, or absorbed into, any porous support.

[0062] It may, for example, be benzoyl peroxide encapsulated in a polymeric system composed of porous microspheres, for instance microsponges marketed under the trademark Microsponges P009A benzoyl peroxide by Cardinal Health.

[0063] The compositions according to the invention also comprise at least one film-forming agent.

[0064] The term "film-forming agent" means an ionic or nonionic hydrophilic polymer having a molecular mass at least greater than 10,000, which, during application to the skin, forms a continuous film. The applicant has demonstrated that these film-forming agents provide the compositions comprised thereof better tolerance.

[0065] Examples of film-forming agents, include the polyvinylpyrrolidones, which are preferably water-soluble, and soluble copolymers thereof, polysaccharides, with the exclusion of cellulose and derivatives thereof, in particular hydroxypropyl cellulose and xanthan gum, polyvinyl alcohols, acrylic copolymers and polyquaterniums.

[0066] Among the polyvinylpyrrolidones and derivatives thereof, exemplary are poly-1-vinyl-2-pyrrolidone, also known as povidone, or the polyvinylpyrrolidone/vinyl acetate copolymer, also known as copovidone, for instance Kollidon® VA64, Kollidon® 30, Kollidon® 90F or Kollidon® K17PF.

[0067] Examples of polysaccharides include the celluloses and derivatives, for instance carboxymethyl cellulose, and also exemplary are the pectins, gums such as karaya gum, and sodium hyaluronate marketed by Contipro.

[0068] Examples of polyvinyl alcohols are polyvinyl alcohols having a degree of polymerization from 500 to 5,000, a degree of hydrolysis from 85 to 89% to a viscosity from 20 to 65 mPa·s (4% (w/w) in water at 20° C.). More specifically, exemplary is Mowiol 40-88 marketed by Sigma Aldrich which has a degree of polymerization of 4200, a degree of hydrolysis from 86.7 to 88.7% to a viscosity from 38 to 42 mPa·s (4% (w/w) in water at 20° C.).

[0069] Among the acrylic copolymers, exemplary are the acrylates/dimethylaminoethyl methacrylate copolymer marketed under the trademark Eudragit E100 by Rohm & Haas, the acrylates/ammonium methacrylate copolymer marketed under the trademark Eudragit RS100 or Eudragit S100 by Rohm & Haas, the acrylates/octylacrylamide copolymer marketed under the trademark Dermacryl 79 by National Starch.

[0070] Among the polyquaterniums, exemplary are polyquaternium 1, 7 and 10, more particularly the polyquaternium-10 marketed under the trademark Celquat SC240C by National Starch.

[0071] Preferably, the film-forming agent is selected from among polyvinylpyrrolidones, which are preferably water-

soluble, polysaccharides such as sodium hyaluronate, polyvinyl alcohols, acrylic copolymers and polyquaterniums.

[0072] Preferentially, the water-soluble film-forming agents according to the invention are selected from among polyvinylpyrrolidones, which are preferably water-soluble such as, for example Kollidon VA64, Kollidon 30 and Kollidon 90F marketed by BASF, from polysaccharides such as the sodium hyaluronate marketed under the trademark high molecular weight sodium hyaluronate by Contipro, from polyvinyl alcohols such as, for example, Mowiol 40-88 marketed by Sigma-Aldrich, from polyacrylamides such as, for example, Dermacryl 79 marketed by National Starch, from polyquaterniums such as, for example, polyquaternium 10 marketed under the trademark Celquat SC240C by National Starch.

[0073] In the compositions according to the invention, the film-forming agents are included at concentrations of less than or equal to 20%, preferably from 0.5% to 20% by weight, relative to the total weight of the composition, and more preferentially from 0.5% to 10%, and preferably from 0.5% to 6%, and in particular 0.5%, 1%, 2%, 3%, 4% or 6%.

[0074] The presence of at least one film-forming agent allows the tolerance to be improved and is particularly advantageous in the case of formulations comprising adapalene and benzoyl peroxide. The reason for this is that naphthoic acid derivatives may be irritant and may have a dehydrating action on the skin. It is therefore advantageous to reduce the irritation induced to be able to increase the doses.

[0075] The compositions of the present invention may be in any galenic form normally employed for topical application, in particular in the form of aqueous, aqueous-alcoholic or oily dispersions, suspensions, aqueous, anhydrous or lipophilic gels, emulsions (lotions, creams, ointments) of liquid, semi-solid or solid consistency obtained by dispersing a fatty phase in an aqueous phase (O/W) or vice versa (W/O) in the presence or absence of emulsifier, or else microemulsions, microcapsules, microparticles or vesicular dispersions of ionic and/or nonionic type.

[0076] Preferably, the compositions according to the invention are in the form of emulsions (lotions, creams or emulsifier-free creams), suspensions or gels, and more preferentially in the form of gels and emulsions.

[0077] Those skilled in the art will take care to select the excipients constituting the compositions according to the invention according to the desired galenic form and such that the advantageous properties of the composition according to the invention are respected.

[0078] The compositions of gel type according to the invention may also in particular comprise one or more of the following ingredients:

[0079] a) one or more gelling agents and/or suspending agents and/or pH-independent gelling agents;

[0080] b) optionally, one or more chelating agents;

[0081] c) optionally, one or more emollients and/or humectants;

[0082] d) one or more wetting agents;

[0083] e) one or more additives.

[0084] The compositions of emulsion (cream, lotion, emulsifier-free cream) type according to the invention may also in particular comprise one or more of the following ingredients:

[0085] a) one or more gelling agents and/or suspending agents and/or pH-independent gelling agents;

[0086] b) optionally, one or more chelating agents;

[0087] c) optionally, one or more emollients and/or humectants;

[0088] d) one or more lipophilic excipients making up the fatty phase;

[0089] e) optionally, one or more emulsifiers;

[0090] f) one or more wetting agents;

[0091] g) one or more additives.

[0092] Representative gelling agents and/or suspending agents and/or pH-independent gelling agents that may be included in the compositions according to the invention, exemplary are the acrylates/C10-30 alkyl acrylate crosspolymer marketed under the trademark Pemulen TR-1 or Pemulen TR-2 by Noveon, the "electrolyte-insensitive" carbomers marketed under the trademark Ultrez 20®, Ultrez 10®, Carbopol 1382®, Carbopol ETD2020NF®, Carbopol 980® or Carbopol 981® by Noveon, polysaccharides, non-limiting examples of which include xanthan gum such as Xantural 180® marketed by Kelco, gellan gum marketed under the trademark Kelcogel® by Kelco, guar gum, cellulose and derivatives thereof such as the microcrystalline cellulose and sodium carboxymethyl cellulose marketed under the trademark Avicel CL-611 by FMC Biopolymer, hydroxypropyl methyl cellulose, in particular the product marketed under the trademark Methocel E4M premium by Dow Chemical, or hydroxyethyl cellulose, in particular the product marketed under the trademark Natrosol IIIIX 250® by Aqualon, the family of magnesium aluminum silicates, such as the Veegum K marketed by Vanderbilt, the family of acrylic polymers coupled to hydrophobic chains, such as the PEG-150/decyl/SMDI copolymer marketed under the trademark Aculyn 44 (polycondensate comprising, as elements, at least one polyethylene glycol containing 150 or 180 mol of ethylene oxide, decyl alcohol and methylenebis(4-cyclohexylisocyanate) (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 marketed under the trademark Structure Solanace, or else mixtures thereof, and the gelling agents of the polyacrylamide family, such as the sodium acryloyldimethyltaurate copolymer/isohexadecane/polysorbate 80 mixture marketed under the trademark Sepineo P 600® (or Simulgel 600 PHA®) by Seppic, the polyacrylamide/C13-14 isoparaffin/laureth-7 mixture, for instance that marketed under the trademark Sepigel 305 by Seppic, the family of carrageenans, in particular divided up into four main families: κ, λ, β, ω, such as Viscarin® and Gelcarin® marketed by IMCD.

[0093] The gelling agents as described above may be incorporated at the preferred concentrations ranging from 0.001% to 15%, and more preferentially ranging from 0.15% to 5%.

[0094] Preferred gelling agents, include the family of carbomers and in particular Carbopol Ultrez-20® and Carbopol ETD 2020®, the family of polyacrylamides and in particular the sodium acryloyldimethyltaurate copolymer/isohexadecane/polysorbate 80 mixture marketed under the trademark Sepineo P 600® (or Simulgel 600 PHA®), the family of polysaccharides and in particular the xanthan gum marketed under the trademark Xantural 180®, the family of celluloses and derivatives thereof and in particular the hydroxyethyl cellulose marketed under the trademark Natrosol 250HHX® and the hydroxypropyl methyl cellulose marketed under the trademark Methocel E4M Premium®, the family of acrylic polymers coupled to hydrophobic chains and in particular the PEG-150/decyl/SMDI copolymer marketed under the trademark Aculyn 44®.

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