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STABLE BENZOYL PEROXIDE COMPOSITION

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ABSTRACT OF THE DISCLOSURE

A therapeutic composition for the treatment of acne comprising a uniform dispersion of benzoyl peroxide in a fluid medium containing water and at least one organic emollient is disclosed. The composition contains from about 1 to 25% by weight benzoyl peroxide, from about 2 to 25% by weight of the organic emollients and from about 50 to 90% by weight water. The organic emollient constituents of the composition are saturated organic compounds that are inert, non-polar and non-ionic with respect to the other constituents of the composition and that have a boiling point higher than water, whereby the composition is stable in storage without the addition of a stabilizer thereto.

BACKGROUND OF THE INVENTION

This is a continuation-in-part of our co-pending United States patent application Ser. No. 538,567, filed Mar. 30, 1966, now abandoned, entitled "Therapeutic Composition."

Acne and seborrhea are conditions of the human skin characterized by an excessive flow of sebum, or skin oil, from the sebaceous glands which are located in the pilosebaceous apparatus. The channel through which sebum reaches the skin surface is the duct of the hair follicle. The presence of excessive amounts of sebum in the duct and on the skin acts to block or stagnate the continuous flow of sebum from the follicular duct, thus producing a thickening of the sebum which becomes a solid plug known as a comedone. When this occurs, hyperkeratinization of the follicular opening is stimulated, thus completely closing the duct. The usual result is a papule, a pustule, or a cyst, often contaminated with bacteria which cause secondary infections. These occurrences characterize the disease state known as acne, and in lesser severity, seborrhea.

Many topical therapeutic agents are employed in the treatment of acne and seborrhea to prevent the blocking of the follicular duct, to reopen the duct once it has become blocked, to act against the infecting bacteria or the thickened sebum, or to provide combinations of each of these actions. The horny outer layer of the skin is formed of dead cells composed largely of a substance known as keratin, and therapeutic agents which act to prevent the blocking of the follicular duct by promoting the removal or sluffing off of excess keratin are known as keratolytic agents. For example, the use of sulfur as a mild cutaneous irritant to remove the horny layer of skin, and with the the debris clogging the follicular openings, is well known in the art, and other substances such as resorcinol and salicylic acid have also long been used as keratolytic agents in the treatment of acne. It has recently been proposed that benzoyl peroxide, which is a powerful oxidizing agent, be employed as an antibacterial and keratolytic agent in the treatment of acne, and an extensive clinical evaluation of this substance has conclusively demonstrated its effectiveness for this purpose when employed by itself or, particularly, when employed in conjunction with finely divided sulfur.

Benzoyl peroxide, $(C_6H_5CO)_2O_2$, is a colorless, odorless, tasteless, crystalline solid that is stable at ordinary room temperatures but which is flammable and is capable of exploding when confined and subjected to grinding heat or flame. It is a powerful oxidizing agent completely non-toxic to man, and because of its lack of local injurious or irritating effects and its lack of penetration into tissue with consequent protein precipitation it has been used topically for its antiseptic and healing properties for many years. More recently, it has been used as a very effective keratolytic and antibacterial agent in the treatment of acne. The material is advantageously incorporated in a cream or ointment base for convenience in applying it to the skin. However, benzoyl peroxide is substantially insoluble in water, and it is ordinarily incorporated in conventional ointments and creams containing water and other common organic and inorganic constituents by first dissolving the peroxide in a volatile organic solvent such as chloroform which is then mixed with the other aqueous and nonaqueous ingredients of the composition. The resulting mixture is then permitted to stand or "age" for several days in order to allow the organic solvent to evaporate from the composition before it is applied to the skin. However, it has been found that when benzoyl peroxide-containing compositions prepared in the manner described are kept at a room temperature for a few days, bubbles of gas evolve indicating that some reaction is taking place between the benzoyl peroxide and the base. Experience has shown that most compositions containing benzoyl peroxide, water and other common organic and mineral components of such preparations display a gradual loss of potency, and that after about four months the level of benzoyl peroxide remaining in the composition is below that necessary to produce the desired therapeutic effects. Any attempt to stabilize the composition by adding antioxidants thereto inhibits the acitivity of the benzoyl peroxide and defeats the purpose of the composition. Consequently, it is the usual practice when preparing therapeutic compositions containing benzoyl peroxide to supply the user with separate packages of benzoyl peroxide and a base formulation which are mixed together just prior to using the composition.

SUMMARY OF THE INVENTION

We have now discovered that compositions containing water, organic emollients and therapeutically effective benzoyl peroxide can be prepared which are stable over a period of time at least equal to the normal commercial life of ordinary pharmaceutical preparations. Moreover, these new compositions display full stability with respect to the benzoyl peroxide component thereof even when subjected to temperatures higher than those normally expected in the ordinary use of the product. The stability of our new benzoyl peroxide-containing composition is predicated on our discovery that if the base or fluid medium in which the benzoyl peroxide is dispersed contains only water and organic emollients which are substantially inert, non-polar and non-ionic with respect to the other constituents of the composition and which have a boiling point higher than water, the benzoyl peroxide constituent thereof will not be decomposed nor react with the base, and therefore will be able to exert its full therapeutic activity as an oxidizing and kerotolytic agent when applied topically to the skin of a patient. The relative proportions of benzoyl peroxide, water and organic emollients present in the compositions are important only insofar as the composition is therapeutically effective and cosmetically acceptable. Accordingly, the composition of our invention comprises a dispersion of finely divided particles of benzoyl peroxide in a water-containing fluid medium that is substantially free of dissolved benzoyl peroxide, the composition con-

taining from about 1 to 25% by weight of benzoyl peroxide, from about 2 to 25% by weight of at least one organic emollient that is substantially inert, non-polar and non-ionic with respect to the other constituents of the composition and from about 50 to 90% by weight water. The composition also advantageously contains from about 1 to 25% by weight finely divided sulfur, as well as emulsifiers for the aqueous and non-aqueous phases of the fluid medium, antibacterial agents, mold growth inhibitors, and the like. Compositions prepared in accordance with our invention possess a stability which far exceeds the normal requirements for a pharmaceutical product, based upon its normally expected commercial life. For example, when our new compositions are stored at 40° C., 100% of the benzoyl peroxide can be recovered at the end of 12 months. This approximates a normal shelf life of eight years.

DETAILED DESCRIPTION

The composition of our invention must contain sufficient benzoyl peroxide to be therapeutically effective, and should not contain more peroxide than can be uniformly dispersed in the fluid base to form a smoothly spreadable cream or ointment. These considerations dictate that the composition contain at least about 1% and not more than about 25% by weight benzoyl peroxide, and we presently prefer that the composition contain from about 5 to about 10% by weight benzoyl peroxide. The benzoyl peroxide constituent of the composition should be of high purity (that is, in the order of 98±1% $(C_6H_5CO)_2O_2$) and in the form of relatively finely divided crystalline particles. High purity benzoyl peroxide in the form of dry crystals having a particle size such that at least 99% will pass thru a 60 mesh screen (Tyler Standard) is available commercially, and this form of the peroxide can be blended directly with the other constituents of the composition, without further reduction in the particle size of the peroxide crystals, to form a finished product. However, we presently prefer to employ a somewhat more coarsely crystalline form of benzoyl peroxide that is packaged wet with water, a fact which greatly increases the safety with which the peroxide can be handled. The wet packed peroxide is dustless, free flowing and disperses readily in the fluid medium comprising the balance of our new composition. The various ingredients of the composition are thoroughly blended together, and the particles of crystalline benzoyl peroxide are simultaneously physically reduced in size, by milling the mixture to obtain a finished composition containing finely divided benzoyl peroxide pursuant to the practice of our invention.

The composition also contains from about 2 to 25% by weight of at least one, and usually several, of certain organic emollients. Specifically, the organic emollient constituents of the composition should be selected from among those which are inert, and which are substantially non-ionic and non-polar, with respect to benzoyl peroxide and the other ingredients of the composition, and further from among those which have a boiling point higher than water. The term "inert" as employed herein refers to organic emollients which do not react chemically with benzoyl peroxide or with the other constituents of the composition at ambient temperature and pressure. In this connection, we have found that the presence of unsaturated carbon atoms in the emollient has an adverse effect on the stability and shelf life of the composition. Accordingly, the emollients preferably should be saturated organic compounds; that is, organic compounds that have no double or triple carbon to carbon atom bonds in the hydrocarbon chain. The terms "non-ionic" and "non-polar" as employed herein refer to emollient organic compounds which are insoluble in water at ordinary temperatures, or if soluble in water do not ionize therein to an appreciable degree. Finally, the requirement that the emollients have a boiling point higher than water

is of importance to insure that some of the emollient will remain on the skin of the patient as a vehicle for the benzoyl peroxide after the evaporation of the water content of the composition therefrom. Emollient compounds meeting these criteria include, but are not limited to, aliphatic alcohols having from 4 to 20 carbon atoms, glycols having 2 to 3 carbon atoms, fatty acids having from 12 to 20 carbon atoms, and the esters of said acids. Specific organic compounds representative of those useful in compositions of our invention include, but are not limited to, butyl alcohol, isobutyl alcohol, amyl alcohol, iso-amyl alcohol, hexyl alcohol, isohexyl alcohol, and the essentially water-insoluble higher aliphatic alcohols which are soluble in or softened by the aforementioned alcohols; ethylene glycol, diethylene glycol, polyethylene glycol, propylene glycol and the like; lauric acid, myristic acid, palmitic acid, stearic acid, and the like; and ethyl laurate, isopropyl laurate, ethyl myristate, n-propyl myristate, isopropyl myristate, ethyl palmitate, isopropyl palmitate, methyl palmitate, methyl stearate, ethyl stearate, isopropyl stearate, butyl stearate, isobutyl stearate, amyl stearate, isoamyl stearate, and the like.

In addition, the composition contains from about 50 to 90% by weight water in which benzoyl peroxide is substantially insoluble. Advantageously, it also contains emulsifiers for the aqueous and non-aqueous phases of the composition, for example, polyethylene glycol 1000 monostearate, as well as preservatives such as methyl paraben (the methyl ester of parahydroxybenzoic acid) to prevent mold growth.

The composition also advantageously contains from about 1 to 25% by weight of finely divided sulfur, and preferably from about 2 to 10% by weight of precipitated sulfur, U.S.P. grade. Sulfur is an antimicrobial and keratolytic agent that has long been used in the treatment of acne. Although it is not known precisely how sulfur exerts its keratolytic effect on the skin, it is through that hydrogen sulfide, which is formed when sulfur is in contact with animal tissue, reacts with alkali in tissue fluids to produce active sulfides which, in turn, promote keratolysis. The combination of precipitated sulfur with benzoyl peroxide produces significantly greater keratolysis than either substance will when used alone. The mechanism responsible for this result is not known. However, it may be that the strong oxidizing properties of benzoyl peroxide facilitate the reaction between the active sulfides and keratin, or benzoyl peroxide may have some direct effect or keratin which makes it more susceptible to the action of the sulfide. In any case, the combination of benzoyl peroxide and sulfur in our new composition gives the composition properties which are especially useful in the treatment of acne.

The composition is prepared by carefully and thoroughly blending the benzoyl peroxide, organic emollient, water and other constituents of the composition. Advantageously, the fluid medium in which the benzoyl peroxide is to be dispersed is first prepared by forming an emulsion of the aqueous and non-aqueous phases of the fluid medium. The benzoyl peroxide and sulfur, if any, constituents of the composition are then added to the emulsion and thoroughly blended therewith to form the therapeutic compostion of our invention. If the benzoyl peroxide constituent is in the form of dry, finely divided crystalline particles no further treatment of the composition is required. However, when the benzoyl peroxide is in the form of relatively coarse crystals packaged wet with water, the mixture of benzoyl peroxide and water is thoroughly mixed with a previously emulsified mixture of the emollient and water constituents of the composition, and the composition is then milled to physically reduce the particle size of the benzoyl peroxide crystals so that substantially all of the particles are smaller than 0.25 mm. in size.

The composition is applied topically to the skin of the patient by rubbing the cream or ointment in well,

once a day, and leaving it on the skin for about two hours after which it is removed by washing with water. If, after two days, treatment remains comfortable, the time of application is increased to four hours daily for four days. Thereafter, nightly applications usually suffice for maintenance as long as no irritation develops. usually at some time within the first four weeks of treatment, a dramatic and suddent generalized peeling or desquamation of the skin occurs in the treated areas. When this occurs, treatment is temporarily discontinued until the reaction subsides, and then application of the composition is resumed at the previous level of treatment.

Almost all persons who use our new composition for the treatment of acne show definite suppression of their eruption within the first few weeks of treatment. The skin first becomes distinctly less oily, and then begins to desquamate. Individuals with minor to moderate papular and pustular acne show prompt suppression of their eruption and usually are well controlled within three months. Individuals with moderately severe acne show a prompt favorable response but require four to six months to obtain good control. Individuals with severe cystic acne, while slower to respond than those with non-cystic acne, obtain excellent suppression of their eruption within six to nine months in all but a few cases.

The following examples are representative but not limitative of therapeutic compositions prepared in accordance with our invention:

(I)	Percent by weight
Benzoyl peroxide	5.0
Stearic acid	6.2
Isopropyl palmitate	3.8
Glyceryl monostearate	4.0
Polyethylene glycol 1000 monostearate	5.2
Propylene glycol	2.2
Methyl paraben	0.1
Deionized water	73.5

(II)	Percent by weight
Benzoyl peroxide	10.0
Palmitic acid	6.2
Isopropyl palmitate	3.8
Glyceryl monostearate	4.0
Polyethylene glycol 1000 monostearate	5.2
Propylene glycol	2.2
Methyl paraben	0.1
Deionized water	68.5

(III)	Percent by weight
Benzoyl peroxide	5.0
Precipitated sulfur	2.0
Stearic acid	6.2
Ethyl stearate	3.8
Glyceryl monostearate	4.0
Polyethylene glycol 1000 monostearate	5.2
Propylene glycol	2.2
Methyl paraben	0.1
Deionized water	71.5

(IV)	Percent by weight
Benzoyl peroxide	5.0
Precipitated sulfur	10.0
Stearic acid	6.2
Isopropyl palmitate	3.8
Glyceryl monostearate	4.0
Polyethylene glycol 1000 monostearate	5.2
Ethylene glycol	2.2
Methyl paraben	0.1
Deionized water	63.5

(V)	Percent by weight
Benzoyl peroxide	5.0
Precipitated sulfur	2.0
Myristic acid	1.6
Amyl stearate	1.0
Glyceryl monostearate	1.0
Polyethylene glycol 1000 monostearate	1.3
Propylene glycol	2.2
Methyl paraben	0.1
Deionized water	85.8

(VI)	Percent by weight
Benzoyl peroxide	5.0
Precipitated sulfur	10.0
Stearic acid	1.6
Isopropyl palmitate	1.0
Glyceryl laurate	1.0
Polyethylene glycol 1000 monostearate	1.3
Propylene glycol	2.2
Methyl paraben	0.1
Deionized water	77.8

(VII)	Percent by weight
Benzoyl peroxide	5.0
Stearic acid	1.9
Palmitic acid	1.2
Isopropyl palmitate	1.2
Glyceryl laurate	1.2
Polyethylene glycol 1000 monostearate	2.5
Propylene glycol	2.5
Methyl paraben	0.1
Deionized water	84.4

(VIII)	Percent by wt.
Benzoyl peroxide	20.0
Lauric acid	1.4
Isoamyl stearate	1.9
Glyceryl monostearate	1.9
Polyethylene glycol 1000 monostearate	1.2
Propylene glycol	2.0
Methyl paraben	0.1
Deionized water	71.5

(IX)	Percent by wt.
Benzoyl peroxide	10.0
Precipitated sulfur	10.0
Stearic acid	0.7
Isopropyl palmitate	0.45
Glyceryl monostearate	0.45
Polyethylene glycol 1000 monostearate	0.6
Diethylene glycol	1.0
Methyl paraben	0.1
Deionized water	76.7

(X)	Percent by wt.
Benzoyl peroxide	20.0
Precipitated sulfur	25.0
Lauryl alcohol	0.4
Isopropyl palmitate	0.3
Glyceryl monostearate	0.3
Polyethylene glycol 1000 monostearate	0.4
Propylene glycol	0.6
Methyl paraben	0.1
Deionized water	52.9

The most widely used composition of our invention contains 5% benzoyl peroxide and 2% sulfur. However, compositions containing 20% benzoyl peroxide and up to 25% sulfur have been used by individuals with dark, very oily skin and by those who have developed resistance to compositions of lesser strength, and compositions containing only 1.25% benzoyl peroxide and 0.5% sulfur have been used by individuals with fair and delicate skin. In all cases the compositions prepared in accordance with our invention are stable and retain full potency of the benzoyl peroxide constituent thereof for a period of time, i.e., for about eight years or more, which far exceeds the normal requirements for a pharmaceutical product.

From the foregoing description of our new composition for the treatment of acne it will be seen that we have made an important contribution to the art to which our invention relates.

We claim:

1. A therapeutic composition for the treatment of acne that is stable in storage without the addition of a stabilizer thereto which consists of a uniform dispersion of finely divided particles of crystalline benzoyl peroxide in a fluid medium consisting essentially of water and an organic emollient selected from the group consisting of saturated aliphatic alcohols having from 4 to 20 carbon atoms, glycols having 2 to 3 carbon atoms, saturated fatty acids having from 12 to 20 carbon atoms, lower alkyl and glyceryl esters of said fatty acids having from 12 to 20 carbon atoms, and mixtures thereof, said organic emollient being inert, non-polar and non-ionic with respect to the other constituents of the composition and that have a boiling point higher than water, said composition containing from about 1 to 25% by weight benzoyl peroxide, from about 2 to 25% by weight of said organic emollient and from about 50 to 90% by weight water.

2. The therapeutic composition according to claim 1 in which the composition contains from about 5 to 10% by weight benzoyl peroxide.

3. The therapeutic composition according to claim 1 in which the composition contains from about 1 to 25% by weight finely divided sulfur.

4. The therapeutic composition according to claim 1 in which the composition contains from about 5 to 10% by weight benzoyl peroxide and from about 2 to 10% by weight finely divided sulfur.

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