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(54) Titre : FORMULATIONS PHARMACEUTIQUES TOPIQUES CONTENANT UNE FAIBLE CONCENTRATION DE PEROXYDE DE BENZOYLE EN SUSPENSION DANS DE L'EAU ET UN SOLVANT ORGANIQUE MISCIBLE AVEC L'EAU

(54) Title: TOPICAL PHARMACEUTICAL FORMULATIONS CONTAINING A LOW CONCENTRATION OF BENZOYL PEROXIDE IN SUSPENSION IN WATER AND A WATER-MISCIBLE ORGANIC SOLVENT

(57) Abrégé/Abstract:
An aqueous formulation for topical application to the skin comprising water, a water-miscible organic solvent, and benzoyl peroxide, wherein the concentration of the organic solvent is sufficient to provide a stable suspension of benzoyl peroxide in the aqueous formulation without the inclusion of a surfactant in the formulation, wherein the ratio of concentrations of water and organic solvent in the formulation is sufficient to maintain the benzoyl peroxide in saturated solubility in the formulation following application to the skin, and wherein the concentration of benzoyl peroxide in the formulation is less than 5.0% and at least 1.0% w/w. The formulation may further contain a chemical compound in addition to benzoyl peroxide that is effective in the treatment of acne. The aqueous formulations of the invention are useful in the treatment of acne and acne rosacea.

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(54) **Title**: TOPICAL PHARMACEUTICAL FORMULATIONS CONTAINING A LOW CONCENTRATION OF BENZOYL PEROXIDE IN SUSPENSION IN WATER AND A WATER-MISCIBLE ORGANIC SOLVENT

(57) **Abstract**: An aqueous formulation for topical application to the skin comprising water, a water-miscible organic solvent, and benzoyl peroxide, wherein the concentration of the organic solvent is sufficient to provide a stable suspension of benzoyl peroxide in the aqueous formulation without the inclusion of a surfactant in the formulation, wherein the ratio of concentrations of water and organic solvent in the formulation is sufficient to maintain the benzoyl peroxide in saturated solubility in the formulation following application to the skin, and wherein the concentration of benzoyl peroxide in the formulation is less than 5.0% and at least 1.0% w/w. The formulation may further contain a chemical compound in addition to benzoyl peroxide that is effective in the treatment of acne. The aqueous formulations of the invention are useful in the treatment of acne and acne rosacea.

TOPICAL PHARMACEUTICAL FORMULATIONS CONTAINING A LOW CONCENTRATION OF BENZOYL PEROXIDE IN SUSPENSION IN WATER AND A WATER-MISCIBLE ORGANIC SOLVENT

Field of the Invention

The present invention pertains to the field of topically applied pharmaceutical formulations for the treatment of dermatologic conditions. In particular, the invention pertains to formulations containing benzoyl peroxide and optionally an anti-acne compound such as an antibiotic.

Background of the Invention

Benzoyl peroxide is commonly used in topical pharmaceutical formulations to treat dermatologic conditions such as acne vulgaris, commonly referred to as acne. Topically applied antibiotics have also been used in topical formulations to treat dermatologic conditions such as acne. Examples of antibiotics that have been used topically to treat acne include macrolide antibiotic such as erythromycin and lincomycin-type antibiotics such as clindamycin and lincomycin.

Combination products containing benzoyl peroxide and an antibiotic have been utilized and provide increased anti-acne efficacy compared to formulations containing either benzoyl peroxide or an antibiotic alone. Klein, U.S. Patent No. 4,497,794, discloses a combination formulation containing benzoyl peroxide and erythromycin for the treatment of acne. Compositions prepared generally as described in Klein '794 are marketed under the tradename Benzamycin® (Dermik Laboratories, Berwyn, PA). Combinations of benzoyl peroxide and lincomycin family antibiotics such as clindamycin are disclosed in Klein, U.S. Patent No. 5,767,098, Baroody, U.S. Patent No. 5,733,886, and Stiefel, U.S. Patent No. 5,466,446. Compositions prepared generally as described in Klein '098 are marketed under the

tradename Benzaclin® (Dermik Laboratories) and as described in Stiefel are marketed under the tradename Duac® (Stiefel Laboratories, Inc., Coral Gables, FL).

One of the problems associated with topical therapy with compositions containing benzoyl peroxide, either alone or in combination with an antibiotic, is the localized irritation at the site of application. Benzoyl peroxide has been shown to have a concentration dependent irritation potential. See Mills et al, International Journal of Dermatology, 25(10):664-667 (1986) and Lassus, Current Medical Research and Opinion, 7(6):370-373 (1981). Each of the above products contains benzoyl peroxide at a concentration of 5% w/w, a concentration that is associated with irritation.

Benzoyl peroxide is practically insoluble in water. The irritation due to application of compositions containing benzoyl peroxide has been determined to be caused by the portion of the benzoyl peroxide that is in suspension, whereas dissolved benzoyl peroxide causes little or no skin irritation. See, Schwarz, U.S. Patent No. 7,153,888; and De Villez, U.S. Patent No. 4,923,900. Schwarz discloses a composition containing benzoyl peroxide wherein all of the benzoyl peroxide of the composition is in solution in an organic solvent. Because dissolution of benzoyl peroxide accelerates the degradation of benzoyl peroxide, Schwarz discloses that an antioxidant is included in the composition to improve the stability of the solution.

One disadvantage of Schwarz is that a high concentration of organic solvent is required in order to dissolve the benzoyl peroxide. High concentrations of organic solvents have a tendency to be irritating to skin, primarily due to the drying effect due to solubilization of skin lipids. In Tables 1 to 3, Schwarz discloses multiple examples of compositions containing various organic solvents and benzoyl peroxide. In each of the examples, the concentration of

organic solvent is more than 10 times, and generally more than 15 times that of the benzoyl peroxide in the composition.

De Villez discloses a composition containing benzoyl peroxide, water, and a water-miscible organic solvent that is less volatile than water and in which the benzoyl peroxide is soluble. Prior to application on the skin, the benzoyl peroxide is in suspension in the composition. However, when applied to the skin, the water from the composition evaporates relatively rapidly compared to the organic solvent. The benzoyl peroxide of the composition is then dissolved *in situ* in the organic solvent, resulting in a solution of benzoyl peroxide after all of the water has evaporated.

In order for the De Villez composition to be transformed from a suspension to a solution, the composition must remain in residence on the skin surface for a sufficient time for the water in the composition to evaporate. During this time, the benzoyl peroxide is in suspension in the composition and the suspended particles are able to interact with the skin to cause irritation. Moreover, De Villez, like Schwarz, requires a relatively high concentration of an organic solvent, which may contribute to the irritation potential of such compositions.

Description of the Invention

It has been surprisingly discovered that substantially similar clinical anti-acne efficacy obtained by use of an aqueous topical formulation containing 5.0% benzoyl peroxide is obtained by providing an aqueous topical formulation containing a suspension of a low concentration of benzoyl peroxide in a saturated solution of water and a water-miscible organic solvent. All % concentrations in this specification refer to % w/w. The formulation of the invention reduces skin irritation due to application of the

formulation compared to application of a similar 5.0% benzoyl peroxide formulation without compromising clinical efficacy.

In one embodiment, the invention is a pharmaceutical formulation for topical application containing water, a water-miscible organic solvent, wherein the ratio of concentrations of the water and the organic solvent is high, and benzoyl peroxide, wherein the concentration of benzoyl peroxide in the formulation is low. As used herein, the term "low concentration", when referring to the concentration of benzoyl peroxide in a formulation, means less than 5.0% w/w. Preferably, the pharmaceutical formulation is an aqueous gel formulation. Preferably, the pharmaceutical formulation is free of surfactants.

The benzoyl peroxide is distributed in the formulation as a uniform suspension. Preferably, the suspended benzoyl peroxide has a mean particle size of less than 100 microns, more preferably between 1 and 50 microns, and most preferably between 2.5 and 30 microns Necessarily, a portion of the benzoyl peroxide will also be dissolved in the organic solvent and a small portion of the benzoyl peroxide will be dissolved in the water. Accordingly, the formulation is a saturated solution of benzoyl peroxide with a dissolved concentration of benzoyl peroxide that is higher than when dissolved in water without the organic solvent.

In a preferred embodiment, but not necessarily, the formulation of the invention contains at least one additional chemical compound that is effective in the treatment of acne. The anti-acne compound may be suspended or dissolved in the formulation. Preferably, the anti-acne compound is soluble in water and so is dissolved in the formulation. One such preferred anti-acne compound is an antibiotic. Preferred antibiotics include those of the macrolide family of antibiotics such as erythromycin, azithromycin, clarithromycin, tilmicosin, and tylosin, and those of the

lincomycin family of antibiotics such as clindamycin and lincomycin. A particularly preferred antibiotic to be used in combination with benzoyl peroxide in the formulation of the invention is clindamycin, such as clindamycin hydrochloride or clindamycin phosphate. Additional topical anti-acne active ingredients that may be contained in the formulation of the invention, either with or without the inclusion of an antibiotic, include salicylic acid, azelaic acid, niacinamide, urea, and retinoids such as tretinoin, adapalene and tazarotene.

The additional anti-acne compound, if present in the formulation of the invention, is preferably present in a concentration in which there is a demonstrable anti-acne effect in the absence of benzoyl peroxide. For example, if clindamycin is present in the formulation of the invention, the concentration of the clindamycin is preferred to be at least 0.5% with a preferred concentration of 1%. Higher concentrations of clindamycin, such as 2.5% or 5.0% or higher may be utilized in the formulation.

The organic solvent of the formulation of the invention has the following characteristics:

(1) is miscible in water,

(2) does not chemically react with benzoyl peroxide at temperatures between 0° C and 40° C,

(3) is a liquid at temperatures between 0° C and 40° C,

(4) is capable of dissolving benzoyl peroxide at a concentration of at least 0.1% at an ambient temperature,

(5) is capable of dispersing benzoyl peroxide in an aqueous gel in the absence of a surfactant.

An example of a preferred organic solvent for the formulation of the invention is a polyol, also known as a polyhydric alcohol. Representative examples of polyols include glycols and sugar alcohols. Preferred polyols for the formulation of the invention include polyether glycols, such

as ethoxydiglycol, and propylene glycol. A preferred water-miscible organic solvent is propylene glycol. The inventors have determined by HPLC analysis that benzoyl peroxide is soluble in 100% propylene glycol at room temperature at a level between 0.2% and 0.3% w/w. A second preferred organic solvent is ethoxydiglycol, such as sold under the tradename Transcutol® (Gattefosse, Saint-Priest, France). It has been determined by HPLC analysis that benzoyl peroxide is soluble in ethoxydiglycol at room temperature at a level of about 4.9%. Another preferred organic solvent is polyethylene glycol, such as PEG 400.

The concentration of the organic solvent in the formulation should be sufficiently high to provide a stable suspension of benzoyl peroxide in an aqueous fluid without the presence of a surfactant. The concentration of the organic solvent should be lower than that which will dissolve all of the benzoyl peroxide in the formulation following the removal of all of the water from the formulation. Generally, the concentration of the organic solvent should be between one and four times the concentration of benzoyl peroxide in the formulation.

Additionally, the ratio of concentrations of water and organic solvent in the formulation should be high, so as to maintain the benzoyl peroxide at or near saturated solubility in the residual formulation, that remaining on the skin after application of the formulation with subsequent evaporation of water from the formulation, thereby maximizing the thermodynamic activity of the benzoyl peroxide in the residual formulation on the skin. It is therefore preferred that, in the formulation of the invention, the relative concentrations of water and the organic solvent should be at least 7:1, such as at least 9:1 or 10:1, preferably at least 12:1, and most preferably at least 20:1, such as up to 98:1.

The concentration of benzoyl peroxide in the formulation is an amount that is less than 5.0% and that is effective to treat the signs and/or symptoms of acne. At the concentrations of benzoyl peroxide in the formulation of the invention, skin irritation is reduced compared to formulations containing 5.0% benzoyl peroxide. Therefore, concentrations of benzoyl peroxide between 1.0% and 4.5% are suitable for invention. A preferred range of benzoyl peroxide concentrations is between 2.0% and 3.5%. A most preferred concentration of benzoyl peroxide is about 2.5%, that is between 2.3% and 2.7%.

The formulation may be one of many topical formulation types containing water as the major ingredient, including solutions, gels, creams, sprays and foams. It is preferred, although not required, that the formulation be in the form of an aqueous gel. Accordingly, the formulation of the invention may contain a gelling or thickening agent. Any gelling agent that is water-dispersible, is suitable for use on epithelial tissue such as skin, and forms an aqueous gel of substantially uniform consistency, is suitable for use in the composition of the invention. One preferred gelling agent is hydroxypropylcellulose, such as that sold under the tradename KLUCEL® (Hercules Incorporated, Wilmington, DE, USA). Another preferred gelling agent is hydroxyethylcellulose, such as that sold under the tradename NATROSOL® (Hercules Incorporated). Other suitable gelling agents include carboxyvinyl polymers, also known as carbomers, such as are sold under the tradename CARBOPOL® 934, 940, 941, 980, and 981 (B.F. Goodrich Co., Akron, OH, USA), ETD 2020™, and ULTREZ® (Noveon, Inc., Cleveland, OH, USA). Additional suitable gelling agents are polyvinyl alcohol, polyethylene oxides, propylene glycol alginates, methylcellulose, hydroxypropylmethylcellulose and natural polymeric gums such as xanthan, and carrageenan. The concentration of gelling agent in the composition may be

varied depending on several factors, including the desired degree of stabilization of the BPO suspension and desired viscosity of the gel composition.

If desired, the formulation of the invention may further include additional pharmaceutically acceptable excipients typically used in formulations and known to those skilled in the art. Such excipients include, for example, humectants, emollients, pH stabilizing agents, preservatives, chelating agents, and anti-oxidants.

The formulation of the invention can be used to treat acne by applying the formulation to affected areas of the skin, such as on the face, neck, back, and chest. The formulation is preferably applied one or more times daily for a time sufficient to ameliorate the signs of acne. It has been surprisingly discovered that the formulation of the invention containing 2.5% benzoyl peroxide has efficacy in treating acne that is comparable to that obtained with formulations containing 5.0% benzoyl peroxide, both preparations containing an antibiotic, clindamycin 1%. It is further surprising that this comparable efficacy was observed when the formulation of the invention was applied only once daily and the formulations containing 5.0% benzoyl peroxide were applied twice daily.

The formulation of the invention may also be used in the treatment of acne rosacea. In treating acne rosacea, the formulation of the invention is applied to affected areas, preferably one or more times daily for a time sufficient to ameliorate the signs and symptoms of acne rosacea.

The formulation of the invention may be made by any means by which the components of the invention are combined to provide a pharmaceutical formulation. For example, a suspension of benzoyl peroxide may be made by combining water, the water-miscible organic solvent, and benzoyl peroxide. Preferably, the combination is mixed, such as by stirring,

sonicating, milling, and/or shaking, to produce a uniform suspension of benzoyl peroxide particles in the water and organic solvent. Additional ingredients, such as a gelling agent and other excipients, may be added either before or after the uniform suspension is obtained.

If an additional anti-acne medication is included in the formulation, it may be combined with the other components prior to or after forming the suspension of benzoyl peroxide. An alternative is to provide a separate aqueous solution of the anti-acne medication, such as clindamycin, and combine this solution with the benzoyl peroxide suspension to obtain a final formulation.

The invention is further illustrated in the following examples which are meant to be exemplary and not limiting.

Example 1 - Exemplary Formulation of the Invention

A pharmaceutical formulation of the invention was made containing the following components as shown in Table 1.

COMPONENT	% w/w
Benzoyl peroxide	2.5
Propylene glycol	5.0
Carbopol 980®	1.75
Potassium hydroxide	0.5
Water	QS 100 (90.25)

Table 1

Example 2 - Exemplary Formulation of the Invention

A pharmaceutical formulation of the invention containing an anti-acne medication in addition to benzoyl

peroxide was made containing the following components as shown in Table 2.

COMPONENT	% w/w
Benzoyl peroxide	2.5
Propylene glycol	5.0
Clindamycin phosphate	1.2*
Carbopol 980®	1.75
Potassium hydroxide	0.5
Water	QS 100 (89.05)

* equivalent to 1.0% clindamycin

Table 2

Example 3 - Comparative Efficacy

The aqueous gel formulation of Example 2 containing 2.5% benzoyl peroxide, 5% propylene glycol, 89% water, and 1% clindamycin was tested for efficacy in the treatment of acne lesions in a large clinical study in which 399 patients were treated. This formulation of the invention is Formulation A. A similar aqueous gel formulation containing 5.0% benzoyl peroxide, 10% propylene glycol, 82.5% water, and 1.0% clindamycin was made and tested for efficacy in the treatment of acne lesions in a second clinical study of very similar design. This formulation, which is not of the invention, is Formulation B. These results were compared with data provided in the prescribing information on the efficacy of an aqueous gel commercial product containing 5.0% benzoyl peroxide, 1% clindamycin, dioctyl sodium sulfosuccinate (surfactant), and water (BenzaClin® Topical Gel, Dermik Laboratories, Bridgewater, NJ). This prior art formulation is Formulation C. Formulations A and B contained no surfactant. Formulation A was applied only once daily whereas Formulations B and C, each of which contain 5.0% benzoyl peroxide, were applied twice daily during the 12 week treatment period. Formulation

A was tested after 12 weeks of application. The data for Formulations B and C is following 10 weeks of application.

Test subjects were instructed to apply the formulation to the face, either twice daily for Formulations B and C or once daily for Formulation A. After 10 weeks for Formulations B and C, and after 12 weeks for Formulation A, the mean percent reduction in inflammatory lesions and non-inflammatory acne lesions was determined. The percentage reduction in inflammatory lesions (pustules and papules) was calculated by subtracting the total inflammatory lesion counts at the end of the study (10 or 12 weeks) from the baseline total inflammatory lesion counts, times 100, and divided by the baseline total inflammatory lesion counts. Non-inflammatory lesions comprised open comedones and closed comedones, and the percentage reduction in non-inflammatory lesions was calculated in the same way. The results of this acne study are shown in Table 3.

	Formulation A	Formulation B	Formulation C
Number of Subjects	399	481	215
Mean % Reduction in Inflammatory Acne Lesions	48.8	59.2	53.5
Mean % Reduction in Non-inflammatory Acne Lesions	42.6	51.0	36.1

Table 3

The data of Table 3 shows that the efficacy of Formulation A containing only 2.5% benzoyl peroxide was similar to that of Formulations B and C. These results are especially surprising in view of the fact that Formulation A

was applied only once daily whereas Formulations B and C were applied twice daily.

Example 4 - Irritation Potential

Formulations A and B of Example 3, each containing benzoyl peroxide and 1.0% clindamycin, were tested to determine the comparative irritation potential of these two formulations. Formulation A of the invention contains 2.5% benzoyl peroxide, propylene glycol at two times the concentration of the benzoyl peroxide, and water at a concentration 17.8 times that of the propylene glycol. Formulation B contains 5.0% benzoyl peroxide, propylene glycol at two times the concentration of the benzoyl peroxide, and water at a concentration 8.25 times that of the propylene glycol.

Gel formulations A and B were applied under separate occlusive patches to the backs of 33 healthy subjects three times a week for three weeks. Each application was observed 48 hours following each application for signs of irritation or inflammation by evaluators and assigned a score using a standardized grading system for irritation on a severity scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). Data from this study shows that use of Formulation A of the invention produced a 33% decrease in overall cumulative irritation score compared to use of Formulation B.

Further modifications, uses, and applications of the invention described herein will be apparent to those skilled in the art. It is intended that such modifications be encompassed in the above description and in the following claims.

CLAIMS

1. An aqueous topical formulation comprising water, propylene glycol, and benzoyl peroxide,

wherein the concentration of the propylene glycol is sufficient to provide a stable suspension of benzoyl peroxide in the aqueous formulation without the inclusion of a surfactant in the formulation,

wherein the formulation is free of surfactant,

wherein the concentration of the propylene glycol is 1 to 4 times the concentration of the benzoyl peroxide in the formulation,

wherein the ratio of concentrations of water and propylene glycol in the formulation is at least 12:1 and is sufficient to maintain the benzoyl peroxide in saturated solubility in the formulation after evaporation of the water, and

wherein the concentration of benzoyl peroxide in the formulation is less than 5.0% and at least 1.0% w/w.

2. The aqueous topical formulation of claim 1 wherein the concentration of benzoyl peroxide is between 2.0% and 3.5% w/w.

3. The aqueous topical formulation of claim 2 wherein the concentration of benzoyl peroxide is about 2.5% w/w.

4. The aqueous topical formulation of claim 1 wherein the concentration of the propylene glycol is lower than that which will dissolve all of the benzoyl peroxide in the formulation following the removal of all of the water from the formulation.

5. The aqueous topical formulation of claim 1 wherein the ratio w/w of water to propylene glycol in the formulation is at least 20:1.

6. The aqueous topical formulation of claim 1 which further comprises a water-dispersible gelling agent.

7. The aqueous topical formulation of claim 1 which further comprises, in addition to benzoyl peroxide, a chemical compound that is effective in the treatment of acne.

8. The aqueous topical formulation of claim 7 wherein the chemical compound is soluble in water.

9. The aqueous topical formulation of claim 7 wherein the chemical compound is an antibiotic.

10. The aqueous topical formulation of claim 9 wherein the antibiotic is a member of the macrolide or lincomycin families of antibiotics.

11. The aqueous topical formulation of claim 10 wherein the antibiotic is clindamycin.

12. A method for making an aqueous topical formulation comprising combining water, propylene glycol, and benzoyl peroxide,

wherein the concentration of the propylene glycol that is combined is sufficient to provide a stable suspension of benzoyl peroxide in the aqueous formulation without the inclusion of a surfactant in the formulation,

wherein the aqueous formulation is free of surfactant,

wherein the concentration of the propylene glycol is 1 to 4 times the concentration of the benzoyl peroxide in the formulation,

wherein the ratio of concentrations of water and propylene glycol that are combined in the formulation is at least 12:1 and is sufficient to maintain the benzoyl peroxide in saturated solubility in the formulation after evaporation of the water,

and wherein the concentration of benzoyl peroxide that is combined in the formulation is less than 5.0% and at least 1.0% w/w.

13. The method of claim 12 wherein the concentration of benzoyl peroxide is between 2.0% and 3.5% w/w.

14. The method of claim 13 wherein the concentration of benzoyl peroxide is about 2.5% w/w.

15. The method of claim 12 wherein the concentration of the propylene glycol that is combined is lower than that which will dissolve all of the benzoyl peroxide in the formulation following the removal of all of the water from the formulation.

16. The method of claim 12 wherein the ratio w/w of water to propylene glycol in the formulation is at least 20:1.

17. The method of claim 12 which further comprises combining a water-dispersible gelling agent in the formulation.

18. The method of claim 12 which further comprises combining a chemical compound, in addition to benzoyl peroxide, that is effective in the treatment of acne.

19. The method of claim 18 wherein the chemical compound is soluble in water.

20. The method of claim 18 wherein the chemical compound is an antibiotic.

21. The method of claim 20 wherein the antibiotic is a member of the macrolide or lincomycin families of antibiotics.

22. The method of claim 21 wherein the antibiotic is clindamycin.

23. Use of an aqueous topical formulation for the manufacture of a medicament for treating acne comprising water, propylene glycol, and benzoyl peroxide,

wherein the concentration of the propylene glycol is sufficient to provide a stable suspension of benzoyl peroxide in the aqueous formulation without the inclusion of a surfactant in the formulation,

wherein the aqueous formulation is free of surfactant, wherein the concentration of the propylene glycol is 1 to 4 times the concentration of the benzoyl peroxide in the formulation,

wherein the ratio of concentrations of water and propylene glycol in the formulation is at least 12:1 and is sufficient to maintain the benzoyl peroxide in saturated solubility in the formulation after evaporation of the water, and

wherein the concentration of benzoyl peroxide in the formulation is less than 5.0% and at least 1.0% w/w.

24. The use of claim 23 wherein the concentration of benzoyl peroxide in the aqueous formulation is between 2.0% and 3.5% w/w.

25. The use of claim 24 wherein the concentration of benzoyl peroxide is about 2.5% w/w.

26. The use of claim 23 wherein the concentration of the propylene glycol is lower than that which will dissolve all of the benzoyl peroxide in the formulation following the removal of all of the water from the formulation.

27. The use of claim 23 wherein the ratio w/w of water to propylene glycol in the formulation is at least 20:1.

28. The use of claim 23 wherein the formulation further comprises a water-dispersible gelling agent.

29. The use of claim 23 wherein the formulation further comprises, in addition to benzoyl peroxide, a chemical compound that is effective in the treatment of acne.

30. The use of claim 29 wherein the chemical compound is soluble in water.

31. The use of claim 29 wherein the chemical compound is an antibiotic.

32. The use of claim 31 wherein the antibiotic is a member of the macrolide or lincomycin families of antibiotics.

33. The use of claim 32 wherein the antibiotic is clindamycin.