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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

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☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Debra D Condino	Date (Optional)	
Name	Debra D. Condino		
Title	Vice President, Allergan, Inc.		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

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This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Ajay P. Parashar Date (Optional): 11/16/2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Varsha Bhatt Date (Optional): 11/15/13

Signature: _____

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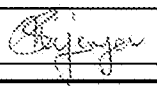
LEGAL NAME OF INVENTOR

Inventor: Vijaya Swaminathan Date (Optional): 11/15/13

Signature: 

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LEGAL NAME OF INVENTOR

Inventor: Kevin S. Warner Date (Optional): 11/16/13

Signature: Kevin S. Warner

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TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF

By

Kevin S. Warner, Ajay P. Parashar, Vijaya Swaminathan, and Varsha Bhatt

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application is a divisional of copending U.S. Patent Application No. 14/082,955, filed on November 18, 2013, which claims the benefit of U.S. Provisional Application Ser. No. 61/728,403 filed on November 20, 2012 and U.S. Provisional Application Ser. No. 61/770,768 filed on February 28, 2013, all of which are incorporated by reference herein in their entirety.

FIELD

[002] The present embodiments relate generally to compositions useful for treating a variety of dermatological conditions. In particular, some embodiments relate to dapsone and dapsone/adapalene compositions and methods for use thereof.

BACKGROUND

[003] Acne is a group of common skin conditions characterized by the so-called "acneiform" or acne-like skin eruptions, which can be contaminated with bacteria, such as Propionibacterium acnes, and can also be marked by inflammation. Acne tends to occur in the areas of skin where the sebaceous glands are most active, such as the face. Acne is associated with psychological trauma, and, if left untreated, can lead to scar formation and disfigurement.

[004] Classification and the diagnosis of various acne conditions can be complex, and even contradictory. Given this complexity and unpredictability, medication and other therapies, are often developed on a trial-and-error basis in order to determine the most effective course of treatment for a particular patient. The outcome of any particular acne treatment regimen greatly varies from patient to patient, as well as throughout treatment of a particular patient. In addition to the complexity and variability of acne conditions, treatment efficacy can be greatly affected by a patient's compliance with the treatment regimen. Patient compliance during acne treatment may be influenced by side effects, which, for

topical medications, commonly include redness, itching, and skin peeling. The complexity of the drug regimen can also negatively affect patient compliance, particularly where two or more different topical medications are prescribed simultaneously. Another factor that negatively affects patient compliance is the cost of a drug regiment, which is considerably higher when multiple medications are prescribed. In some countries, acne is considered a cosmetic problem, and acne treatments are not covered by insurance plans, thus further increasing patient's treatment costs. Certain compositions for treatment of acne are available. Many of the available compositions include one active agent known to have anti-acne activity. Stability of compositions with multiple anti-acne agents can be problematic. Also, these compositions can be difficult to manufacture.

[005] The problems described above are not confined to the treatment or acne, but are also applicable to a variety of other skin conditions, including, but not limited, to conditions or classes of conditions with complex or unknown etiology and that are difficult to classify or diagnose, in which, nevertheless, topical application of agents are known to be effective at least in some cases. Examples of such conditions or classes of conditions include psoriasis, rosacea and ichthyosis.

[006] Accordingly, there is a continuing need for compositions and methods used in a treatment of a variety of skin conditions, such as acne, in which topical application is potentially effective. The compositions and methods provided herein address these and other needs in the art.

SUMMARY

[007] Dapsone, (4,4'-diaminodiphenyl sulfone) is a medicament possessing several beneficial medicinal activities. Dapsone is typically administered as one of the medicinal agents used in the treatment of leprosy. Dapsone and its derivatives are also effective for treatment of bacterial infections, protozoal infections such as malaria, pneumocystis carinii, and plasmonic infections such as toxoplasmosis.

[008] Dapsone is also useful as an anti-inflammatory agent. It has been used to treat skin diseases characterized by the abnormal infiltration of neutrophils, such as Dermatitis herpetiformis, linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum, *acne vulgaris*, and Sweet's Syndrome.

[009] Use of topical compositions of dapsone can be problematic. Topical compositions may act as drying agents for the skin. They remove essential oils and natural skin softeners from the skin thus causing it to be dry, itch and crack. Inclusion of exogeneous

skin emollients, oils and the like, however, causes phase separation and precipitation of dapsone. Use of typical emulsifiers does not solve the dapsone precipitation owing to the lowered dapsone solubility and conflicting physical characteristics of the phases of the resulting composition. In particular, topical compositions including dapsone and methods are needed that would, for example, exhibit improved effectiveness, reduced side effects, or both, when used in a particular patient with a skin condition. Such improved topical compositions including dapsone and methods of their uses are also needed to improve treatment of patients with acne or suspected acne. The present dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. Some useful compositions include dapsone and/or adapalene in a polymeric viscosity builder. Some compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Diethylene glycol monoethyl ether is a solubilizer for dapsone, thereby allowing compositions to be prepared with increased solubilized concentrations of dapsone. As a result, the compositions described herein are effective in treating dermatological conditions in a subject in need thereof.

[010] Moreover, it has been found that use of a polymeric viscosity builder minimizes the intensity of yellowing of the composition caused by the increased solubility of dapsone in diethylene glycol monoethyl ether. In addition, the polymeric viscosity builder influences dapsone crystallization. This, in turn, results in compositions with improved aesthetics (i.e., reduction in particle size which minimizes "gritty" feeling upon application).

[011] In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w.

[012] In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 3% w/w to 8% w/w.

[013] In another embodiment, there are provided methods for treating a dermatological condition. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition described herein.

BRIEF DESCRIPTION OF THE FIGURES

[014] Figure 1 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on color change.

[015] Figure 2 presents the impact of an acrylamide/sodium acryloyldimethyltaurate copolymer emulsion viscosity builder on dapsone crystal growth.

[016] Figure 3 presents the impact of anti-oxidants and chelating agents on color change.

DETAILED DESCRIPTION

[017] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and do not restrict the claims. As used herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[018] Some embodiments include compositions and products for treatment of skin conditions and methods of treating skin conditions. The term "skin condition" as used herein encompasses human and animal conditions, disorders, or diseases affecting skin. Such skin conditions include, but are not limited to, conditions involving skin inflammation, conditions involving sebaceous glands and hair follicles, conditions characterized by acneiform symptoms, and conditions involving skin dryness, skin thickening, skin scaling or skin flaking. Skin conditions that can be treated using some compositions, products and methods described herein include, but are not limited to, acne, rosacea, folliculitis, perioral dermatitis, photodamage, skin aging, psoriasis, ichtiosis, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, scars, including surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, eczema, and miliaria.

[019] The term "acne," as used herein, encompasses skin conditions involving acneiform or acne-like symptoms. For example, a skin condition characterized by follicular eruptions, such as papules and pustules resembling acne, can be categorized as acne. It is to be understood that the term "acne" is not to be limited to diseases and conditions characterized by papules and pustules, but can be characterized by a variety of symptoms. It

is also to be understood that a particular patient having acne can be in remission, or the patient's acne can be controlled by continuing treatments, and therefore the patient can exhibit reduced symptoms or be asymptomatic. Nevertheless, continuing treatment of acne can be recommended in such a patient in order to reduce the probability of the return of the acne symptoms.

[020] Symptoms of acne or acne-like conditions include, but are not limited to, the appearance of various skin lesions. The term "lesion" is generally used to denote an infected or diseased patch of skin. A lesion can involve an infected sebaceous gland. Some lesions are more severe than others. Examples of skin lesions are comedones, macules, papules, pustules, nodules and cysts. The term "comedo" (plural "comedones") is used to describe a sebaceous follicle plugged with dirt, other cells, tiny hairs, or bacteria. Comedones include the so-called "blackheads," which can also refer to as "open comedones," which have a spot or a surface that appears black. Comedones also include slightly inflamed, skin colored bumps, as well as "whiteheads," which have a spot or a surface that appears white. The term "macule" generally refers to a flat spot or area of the skin with a changed color, such as a red spot. The term "pustule" is generally used to refer to an inflamed, pus-filled lesion, or a small inflamed elevation of the skin that is filled with pus. The term "papule" is generally used to refer to a small, solid, usually inflammatory elevation of the skin that does not contain pus. The term "nodule" is generally used to refer to an elevation of a skin that is similar to a papule but is white and dome-shaped. Colloquially, a papule, a pustule or a nodule can be referred to as "a pimple" or "a zit." The term "cyst" generally refers to an abnormal membranous sac containing a liquid or semi-liquid substance containing white blood cells, dead cells, and bacteria. Cysts can be painful and extend to deeper layers of skin.

[021] In dermatological science and dermatological and cosmetology practice, acne can be classified or categorized into one or more types or categories, according to one or more lines of categorization, such as a predominantly observed type of symptoms, severity of condition or predominant localization. It is to be understood that classification of acne into one of the subtypes does not mean that the characteristics of the classified condition are limited to the symptoms associated with the specific type.

[022] Comedonal acne is characterized by the appearance of non-inflammatory lesions, such as blackheads and whiteheads. Localized cystic acne is characterized by appearance of a few cysts on face, chest and back. Diffuse cystic acne is characterized by the appearance of cysts on wide areas of face, chest and back. Nodular acne is characterized by the appearance of nodules. Nodulocystic acne is characterized by appearance of nodules

and cysts. *Acne vulgaris* is a common form of acne characterized by the appearance of several types of lesions, which may appear together or separately. Individual acne lesions usually last less than two weeks but the deeper papules and nodules may persist for months. *Acne vulgaris* commonly affects adolescents, but it may also appear, persist or become more severe in adulthood. *Acne vulgaris* may occur on the face, chest, back and sometimes even more extensively.

[023] Depending on severity, acne can be mild, moderate or severe. Mild acne is generally categorized by the appearance of with blackheads and whiteheads, but can also include papules and pustules. Moderate acne is generally characterized by appearance of more painful, deep-rooted, inflamed lesions, which can result in scarring. Severe acne is characterized by the appearance of deep-rooted inflammatory lesions, including cysts and nodules which can be painful and can produce scarring. Acne conglobata is a category of acne characterized by highly inflammatory cysts that communicate under the skin with abscesses and burrowing sinus tracts.

[024] Some other skin conditions exhibiting acne-like symptoms which can be treated by the compositions and methods described herein are discussed below. Pyoderma faciale, also known as rosacea fulminans, is a condition that appears in females and is characterized by abrupt appearance of inflamed cysts and nodules localized on the face. Rosacea, which can be referred to as acne rosacea, is a condition that can affects both the skin and the eyes and is characterized by redness, bumps, pimples, and, in advanced stages, thickened skin on the nose. In some classification systems, rosacea and acne are considered as separate conditions. Rosacea usually occurs on the face, although the neck and upper chest are also sometimes involved. A mild degree of eye (ocular) involvement occurs in more than fifty percent of people with rosacea. Perioral dermatitis is characterized by the appearance of small tiny papules, pustules, red bumps and scaling with intense itching. It is usually localized to the surrounding area of the mouth and on the chin, or extends to involve the eyelids and the forehead. Gram-negative folliculitis is a bacterial infection characterized by the appearance of pustules and cysts, possibly occurring as a complication resulting from a long term antibiotic treatment of *acne vulgaris*.

[025] As used herein, the terms “treatment” or “treating” in reference to a skin condition generally mean “having positive effect on a skin condition” and encompass alleviation of at least one symptom of a skin condition, a reduction in the severity of the skin conditions, or delay, prevention, or inhibition of the progression of the skin condition. Treatment need not mean that the condition is totally cured. A composition or a product

useful for treatment of a skin condition, or a method of treating a skin condition, needs only to reduce the severity of a skin condition, reduce the severity of symptoms associated therewith, provide improvement to a patient's quality of life, or delay, prevent, or inhibit the onset of symptoms of a skin condition.

[026] In one embodiment, there are provided compositions including dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present at a concentration of about 5% w/w to about 10% w/w, about 1% w/w to about 10% w/w, about 3% w/w to about 10% w/w, about 3% w/w to about 8% w/w, about 4% w/w to about 6% w/w, or about 5%. In certain embodiments, dapsone is present in the composition at 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, or 10.0% w/w.

[027] In some embodiments, the polymeric viscosity builder is an acrylamide/sodium acryloyldimethyltaurate copolymer, and further includes isohexadecane, sorbitan oleate, water, and Polysorbate 80. In some embodiments, the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w. In some embodiments, the polymeric viscosity builder is present at a concentration of about 3% w/w to about 5% w/w. In some embodiments, the polymeric viscosity builder is present in the composition at about 4% w/w.

[028] In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 25% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 30% w/w to about 40% w/w. In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 35% w/w to about 40% w/w.

[029] In some embodiments, diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w, about 20% w/w to about 30% w/w, or about 25%.

[030] In another embodiment, there are provided compositions further including adapalene. In some embodiments, adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

[031] In some embodiments, the second solubilizing agent is selected from alcohols, glycols, esters, ethers, or silicones. Such second solubilizing agents include, but are not limited to, PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, benzyl alcohol, diethyl sebacate, and ethanol.

[032] In certain embodiments, the second solubilizing agent is propylene glycol. In some embodiments, propylene glycol is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene glycol is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene glycol is present in the composition at about 5% w/w.

[033] In certain embodiments, the second solubilizing agent is propylene carbonate. In some embodiments, propylene carbonate is present at a concentration of about 2% w/w to 8% w/w. In some embodiments, propylene carbonate is present at a concentration of about 3% w/w to 7% w/w. In some embodiments, propylene carbonate is present in the composition at about 5% w/w.

[034] In certain embodiments, the second solubilizing agent is ethanol. In some embodiments, ethanol is present at a concentration of about 1% w/w to about 5% w/w. In some embodiments, ethanol is present at a concentration of about 2% w/w to about 4% w/w. In some embodiments, ethanol is present in the composition at about 3% w/w.

[035] In some embodiments, the compositions further include methyl paraben.

[036] In other embodiments, the compositions further include carbomer homopolymer type C. In some embodiments, carbomer homopolymer type C is present at a concentration of about 0.7% w/w to about 1.5% w/w. In other embodiments, carbomer homopolymer type C is present at a concentration of about 0.85% w/w to about 1.0% w/w.

[037] In some embodiments, the compositions further include a neutralizing agent. In certain embodiments, the neutralizing agent is an ionic or amine buffer. In certain embodiments, the neutralizing agent is sodium hydroxide or triethanolamine. Use of a neutralizing agent results in compositions typically having a pH from 5.5 to 6.5.

[038] In some embodiments, the compositions further include a chelating agent. In some embodiments, the chelating agent is ethylene diamine tetraacetic acid (EDTA). EDTA is typically present in the compositions from about 0.02% w/w to about 0.04% w/w. In certain embodiments, EDTA is present in the compositions at about 0.03% w/w.

[039] Compositions described herein are typically in the form of a gel, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

EMBODIMENTS

[040] The following embodiments are specifically contemplated herein.

Embodiment 1. A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing

agent, a polymeric viscosity builder, and water, wherein the dapsone is present in the composition at a concentration of about 3% w/w to about 10% w/w.

Embodiment 2. The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w.

Embodiment 3. The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 20% w/w to about 30% w/w.

Embodiment 4. The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present in the composition at a concentration of about 25% w/w.

Embodiment 5. The composition of embodiment 1, further comprising adapalene.

Embodiment 6. The composition of embodiment 5, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 7. The composition of embodiment 1 wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 8. The composition of embodiment 1, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 9. The composition of embodiment 8, wherein the second solubilizing agent is propylene glycol.

Embodiment 10. The composition of embodiment 9, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 11. The composition of embodiment 8, wherein the second solubilizing agent is propylene carbonate.

Embodiment 12. The composition of embodiment 11, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 13. The composition of embodiment 8, wherein the second solubilizing agent is ethanol.

Embodiment 14. The composition of embodiment 13, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 15. The composition of embodiment 1, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 16. The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 17. The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 18. The composition of embodiment 1, further comprising methyl paraben.

Embodiment 19. The composition of embodiment 1, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 20. The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 21. The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 22. The composition of embodiment 19, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 23. The composition of embodiment 19, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 24. The composition of embodiment 1, further comprising a neutralizing agent.

Embodiment 25. The composition of embodiment 24 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 26. The composition of embodiment 1 further comprising a chelating agent.

Embodiment 27. The composition of embodiment 26, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 28. The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 29. The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 30. The composition of embodiment 1 wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 31. A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1.

Embodiment 32. The method of embodiment 31 wherein the condition is *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 33. The method of embodiment 32 wherein the condition is *acne vulgaris.*

Embodiment 34. The composition of embodiment 1, 2, 3, or 4, further comprising adapalene.

Embodiment 35. The composition of embodiment 34, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 36. The composition of embodiment 1, 2, 3, 4, 34, or 35, wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 37. The composition of embodiment 1, 2, 3, 4, 34, 35, or 36, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide,

propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 38. The composition of embodiment 37, wherein the second solubilizing agent is propylene glycol.

Embodiment 39. The composition of embodiment 38, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 40. The composition of embodiment 37, wherein the second solubilizing agent is propylene carbonate.

Embodiment 41. The composition of embodiment 40, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 42. The composition of embodiment 37, wherein the second solubilizing agent is ethanol.

Embodiment 43. The composition of embodiment 42, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 44. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 45. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, or 44, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 46. The composition of embodiment 45, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 47. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46, further comprising methyl paraben.

Embodiment 48. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 49. The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 50. The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 51. The composition of embodiment 48, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 52. The composition of embodiment 48, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 53. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, further comprising a neutralizing agent.

Embodiment 54. The composition of embodiment 53 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 55. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54, further comprising a chelating agent.

Embodiment 56. The composition of embodiment 55, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 57. The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 58. The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 59. The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 60. A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a

composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 61. The method of embodiment 60 wherein the condition is *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 62. The method of embodiment 60 wherein the condition is *acne vulgaris.*

[041] The following examples are intended only to illustrate the some embodiments and should in no way be construed as limiting the claims.

EXAMPLES

Example 1

[042] Table 1 lists two formulations (containing equivalent levels of diethylene glycol monoethyl ether) that show the impact of acrylamide / sodium acryloyldimethyltaurate copolymer based thickener on dapsone particle size. Figure 2 presents impact of acrylamide / sodium acryloyldimethyltaurate copolymer based thickener on dapsone crystal growth. The microscopic image of ENA (30% diethylene glycol monoethyl ether, 4% acrylamide / sodium acryloyldimethyltaurate copolymer based thickener) in comparison to ENC (30% diethylene glycol monoethyl ether, 1% Carbopol 980) shows a clear difference in particle size of the dapsone. Larger crystals were observed in the sample with carbomer homopolymer type C (ENC vs. ENA).

Table 1 **Formulations Tested For Dapsone Crystal Size**

Formulation #	ENA	ENC
Dapsone	7.5	7.5
Diethylene glycol monoethyl ether	30	30
Carbomer homopolymer type C.	--	1
acrylamide / sodium acryloyldimethyltaurate copolymer based thickener	4	--
Methyl paraben	0.2	0.2
pH adjusting solution	pH 5.5-7	pH 5.5-7
Purified Water	Q.S 100	Q.S 100

Example 2

Example compositions contemplated for use as described herein are set forth in Table 2 below:

Table 2.

Composition #	1	2	3	4	5	6	7	8	9	10
Dapsone	5-10									
Adapalene	---					0.1-0.3				
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
Carbomer homopolymer type C	---			0.85-1.5		---	---	---	0.85-1.5	
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	4			---		4			---	
Methyl paraben	0.2									
NaOH/ pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 3

[043] Anti-oxidants and chelating agents such as sodium metabisulfite, citric acid and EDTA were added to formulations to help slow down or completely stop any impurity formation. Table 3 presents the composition of formulations tested. Formulation A7 with sodium metabisulfite minimized the intensity of yellow color caused by the increased solubility of dapsone in diethylene glycol monoethyl ether and maintained the low color intensity over time at accelerated condition (40^0C). See Figure 3 for appearance of the

formulations over 4 weeks. Table 4 presents the formulation panel summarizing other formulation options with chelating agents and antioxidants.

Table 3. Compositions Tested containing Antioxidants or Chelating Agents

Composition #	**A5**	**A6**	**A7**
Dapsone	7.5		
Diethylene glycol monoethyl ether	35	40	35
carbomer homopolymer type C	1.25	---	1.25
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	---	4	---
EDTA	0.05		---
Anhydrous Citric Acid	0.1		---
Sodium Metabisulfite	---		0.2
Methyl paraben	0.17		0.2
Propyl paraben	0.03		---
NaOH/ pH adjusting solution	pH 5.5-6.5		
Purified Water	Q.S 100		

Table 4. Formulation panel summarizing other formulation options

Composition #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Dapsone	5-10									
Adapalene	---					0.1-0.3				
Diethylene glycol monoethyl ether	30	35	40	30	35	30	35	40	30	35
carbomer homopolymer type C	---			0.85-1.5		---			0.85-1.5	
Acrylamide/sodium Acryloyldimethyltaurate copolymer emulsion	4			---		4			---	
EDTA	0-0.1									
Citric Acid	0-0.1									
Sodium Metabisulfite	0-0.5									
Methyl paraben	0.2									
NaOH/ pH adjusting solution	pH 5.5-6.5									
Purified Water	Q.S 100									

Example 4

[044] Additional example compositions contemplated for use as described herein are set forth in Table 5 below.

Table 5 Additional examples containing alternate neutralizer

Materials	% w/w					
	5-1	**5-2**	**5-3**	**5-4**	**5-5**	**5-6**
Dapsone	7.5					
Adapalene	---			0.3		--
Diethylene glycol monoethyl ether	30	35	40	30	40	25
carbomer homopolymer type C	1					
Methylparaben	0.2					
Triethanolamine (TEA) Q.S.	pH 5.5-6.5					
Hydrochloric Acid Q.S	pH 5.5-6.5					
Purified Water	q.s.a.d.100					

Example 4

[045] Additional example compositions contemplated for use as described herein are set forth in Table 6 below.

Table 6 Additional examples (containing co-solvents, stabilizer and alternate thickener)

	% w/w					
Materials	**6-1**	**6-2**	**6-3**	**6-4**	**6-5**	**6-6**
Dapsone	7.5		10	7.5		
Adapalene	--	0.3				
Diethylene glycol monoethyl ether	25	35	35	25	30	40
Propylene glycol	5					
Propylene Carbonate	5					
Ethanol (absolute)	3			--	3	
EDTA	0.03					
Carbomer Interpolymer Type A	--			1.5		
Carbomer Interpolymer Type B	--			0.3		
Acrylamide/sodium acryloyldimethyltaurate copolymer emulsion	4			--		4
Methyl Paraben	0.2					
Triethanolamine	--			Q.S. pH 5.5 - 6.5		
Purified Water	q.s.a.d.100					

Example 5

[046] Another useful composition is depicted in Table 7.

Table 7

Ingredient	**Amount (% w/w)**
Dapsone	5-8
Adapalene	0.1-0.3
Diethylene glycol monoethyl ether	40.00
Propylene glycol	5.00
Ethanol (absolute)	3.00
Ethylene Diamine Tetraacetic acid (EDTA)	0.03
Methyl Paraben	0.20
Sepineo P 600	4.00
Purified Water	Q.S.

Example 6

[047] Another useful composition is depicted in Table 8.

Table 8

Ingredient	**Amount (% w/w)**
Dapsone	5.0
Diethylene glycol monoethyl ether	25
Methyl Paraben	0.2
Carbopol 980	0.85
Sodium Hydroxide	0.2
Purified Water	Q.S.

[048] While this some embodiments have been described with respect to these specific examples, it is understood that other modifications and variations are possible without departing from the spirit of the invention. Each and every reference identified herein is incorporated by reference in its entirety.

WHAT IS CLAIMED IS:

1. A method for treating a dermatological condition comprising administering to a subject in need thereof a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

2. The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. The method of claim 1 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

6. The method of claim 5 wherein the condition is acne vulgaris.

7. A method for treating a dermatological condition comprising administering to a subject in need thereof a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

8. The method of claim 7, wherein the topical pharmaceutical composition further comprises methyl paraben.

9. The method of claim 7 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

10. The method of claim 9 wherein the condition is acne vulgaris.

ABSTRACT

Dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. The compositions of this disclosure include dapsone and/or adapalene in a polymeric viscosity builder. Subject compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Use of the polymeric viscosity builder provides compositions with increased concentrations of diethylene glycol monoethyl ether relative to compositions without the polymeric viscosity builder.

Figure 1. Appearance of formulations following 4 weeks of storage

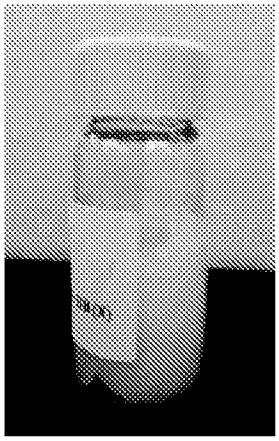
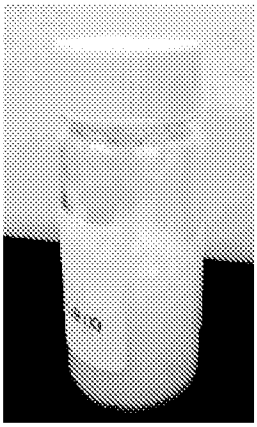
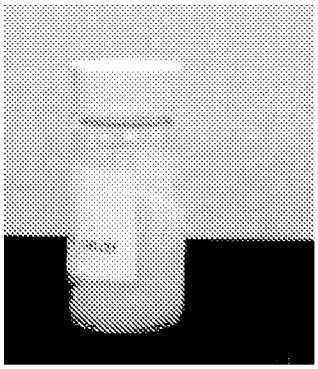
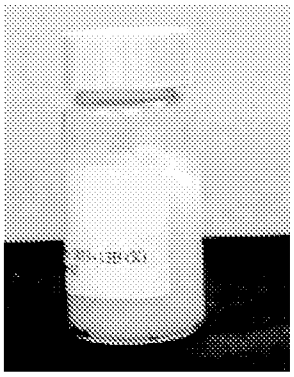
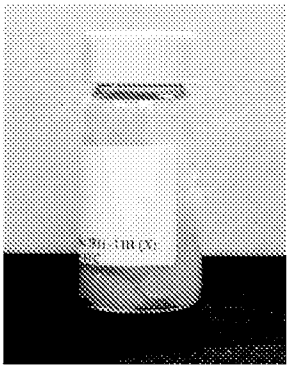
A1 at initial timepoint 	**A2 at initial timepoint** 
A1 after 4 weeks storage at 25^{0}C 	**A2 after 4 weeks storage at 25^{0}C** 
A1 after 4 weeks storage at 40^{0}C 	**A2 after 4 weeks storage at 40^{0}C** 

Figure 2. Polarized light images of dapsone in suspension formulations

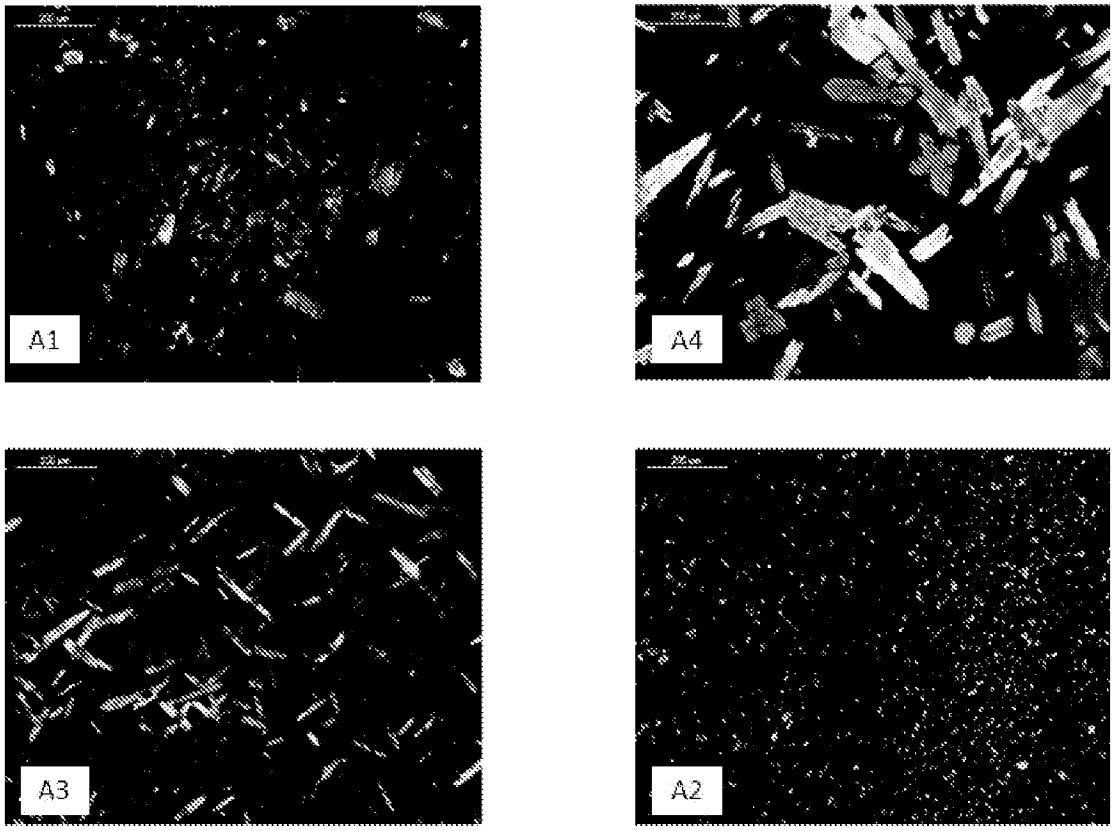
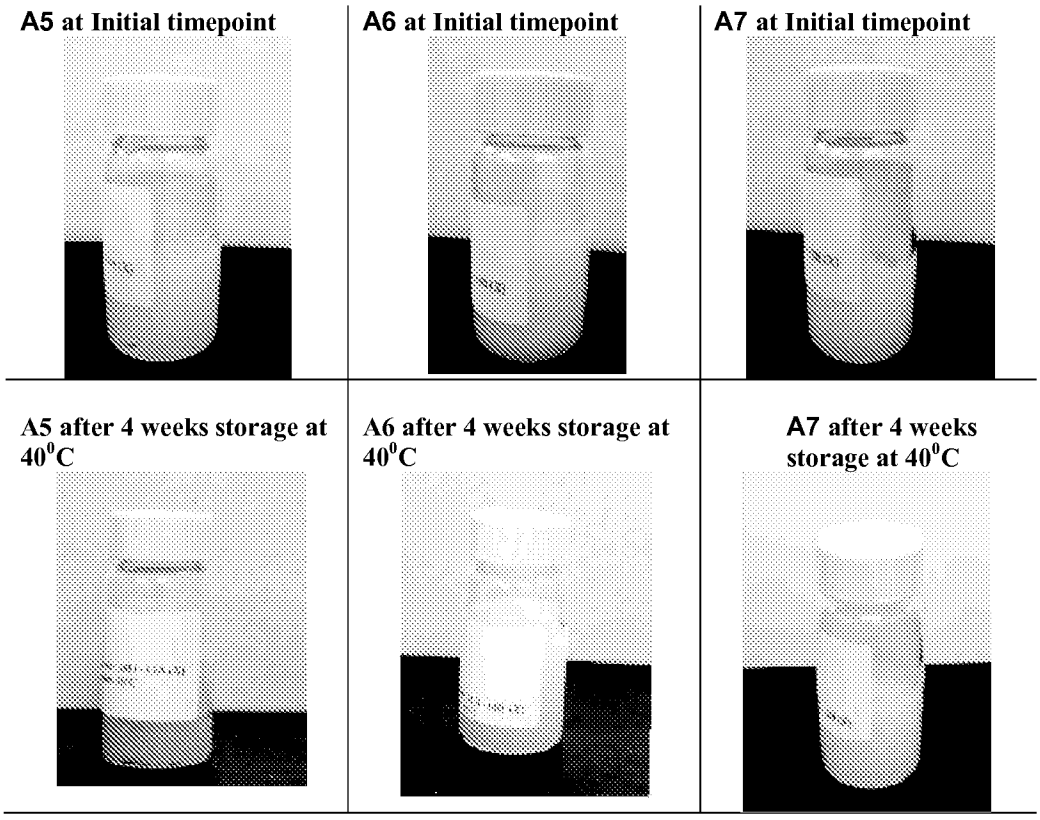


Figure 3. Appearance of formulations with antioxidants or chelating agents over 4 weeks



Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	19107DIV(AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1600**

Electronic Acknowledgement Receipt

EFS ID:	23813364
Application Number:	14885805
International Application Number:	
Confirmation Number:	9004
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
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Filer:	Laura Lee Wine/Maria Stein
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Attorney Docket Number:	19107DIV(AP)
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Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1600
RAM confirmation Number	4898
Deposit Account	010885
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	19107DIV_ADS.pdf	1819530 a7c5ffed9c99fb670719d276be10973ff81f596e	no	8
Warnings:					
Information:					
2		19107DIV_FilingPapers.pdf	4780615 4bffad03b63bfb130ecacefa8c6032167b2c3ad4	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Power of Attorney	1	1
Oath or Declaration filed	2	2
Oath or Declaration filed	3	3
Oath or Declaration filed	4	4
Oath or Declaration filed	5	5
Specification	6	23
Claims	24	25
Abstract	26	26
Drawings-other than black and white line drawings	27	29

Warnings:					
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EFS ID:	23813364
Application Number:	14885805
International Application Number:	
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Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
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Filing Date:	
Time Stamp:	18:23:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1600
RAM confirmation Number	4898
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	19107DIV_ADS.pdf	1819530 a7c5ffed9c99fb670719d276be10973ff81f596e	no	8
Warnings:					
Information:					
2		19107DIV_FilingPapers.pdf	4780615 4bffad03b63bfb130ecacefa8c6032167b2c3ad4	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Power of Attorney	1	1
Oath or Declaration filed	2	2
Oath or Declaration filed	3	3
Oath or Declaration filed	4	4
Oath or Declaration filed	5	5
Specification	6	23
Claims	24	25
Abstract	26	26
Drawings-other than black and white line drawings	27	29

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	35247 ee187676e0a0335a55a5b1ac1d9517d9edabbed7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6635392		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kevin	S.	Warner	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Anaheim	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	1281 N. Walden Lane		
Address 2			
City	Anaheim	State/Province	CA
Postal Code	92807	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ajay	P.	Parashar	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Fairfax	State/Province	VA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	12788 Heron Ridge Drive		
Address 2			
City	Fairfax	State/Province	VA
Postal Code	22030	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Vijaya		Swaminathan	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

City	San Francisco	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	358 22nd Avenue, Apt. 1		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94121	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Varsha		Bhatt	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	San Francisco	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	180 Mallorca Way, Apt. 104		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94123	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	051957		
Email Address	allergan_docketing@cpaglobal.com	Add Email	Remove Email

Application Information:

Title of the Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF		
Attorney Docket Number	19107 DIV (AP)	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	3	Suggested Figure for Publication (if any)	

Filing By Reference :

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	051957		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	14082955	2013-11-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14082955	Claims benefit of provisional	61728403	2012-11-20
Prior Application Status	Expired		Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14082955	Claims benefit of provisional	61770768	2013-02-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country	Filing Date (YYYY-MM-DD)	Access Code (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

PTO/AIA/14 (07-14)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Allergan, Inc.

Mailing Address Information For Applicant:

Address 1	2525 Dupont Drive		
Address 2			
City	Irvine	**State/Province**	CA
Country [i]	US	Postal Code	92612
Phone Number	(714) 246-6996	Fax Number	(714) 246-4249

PTO/AIA/14 (07-14)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

Email Address	allergan_docketing@cpaglobal.com

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature	/Laura L. Wine/			Date (YYYY-MM-DD)	2015-10-16
First Name	Laura	Last Name	Wine	Registration Number	68681

Additional Signature may be generated within this form by selecting the Add button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107 DIV (AP)
	Application Number	
Title of Invention	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent C o o p eration Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

SCORE Placeholder Sheet for IFW Content

Application Number: 14885805 Document Date: 10/16/2015

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

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- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/885,805

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	10 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/885,805	10/16/2015	1629	1600	19107 DIV (AP)	10	2

CONFIRMATION NO. 9004

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

FILING RECEIPT

OC000000078335219

Date Mailed: 10/30/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Kevin S. Warner, Anaheim, CA;
Ajay P. Parashar, Fairfax, VA;
Vijaya Swaminathan, San Francisco, CA;
Varsha Bhatt, San Francisco, CA;

Applicant(s)

Allergan, Inc., Irvine, CA;

Power of Attorney: The patent practitioners associated with Customer Number 051957

Domestic Priority data as claimed by applicant

This application is a DIV of 14/082,955 11/18/2013 PAT 9161926
which claims benefit of 61/728,403 11/20/2012
and claims benefit of 61/770,768 02/28/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 10/28/2015
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/885,805**

Projected Publication Date: 02/04/2016

Non-Publication Request: No

Early Publication Request: No

Title

TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

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EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/885,805	Applicant(s) WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☒ Claim(s) *5,9* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-10 are presented for examination.

Acknowledgement is made of the present application as a divisional (DIV) application of U.S. Patent Application No. 14/082,955, filed November 18, 2013, now U.S. Patent No. 9,161,926, which claims benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application Nos. 61/728,403, filed November 20, 2012, and 61/770,768, filed February 28, 2013.

Objections to the Claims

Claims 5 and 9 are objected to for reciting "eczema" twice in the claim. Correction is required.

Claims 5 and 9 are objected to for misspelling the term "pilaris" as "piralis". Correction is required.

Claim Rejections - 35 USC § 112(a) (Pre-AIA First Paragraph), Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any other dermatological condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art.

Note that the specification must be enabling as of the filing date. MPEP §2164.05(a).

Applicant's instant claims are directed to a method for the treatment of any dermatological condition by administering a topical pharmaceutical composition comprising about 7.5% w/w dapsone; about 30% w/w to about 40% w/w diethylene glycol monoethyl ether; about 2% w/w to about 6% w/w acrylamide/sodium acryloyldimethyl taurate copolymer; and water, and further wherein the composition does not comprise adapalene (claim 1). Applicant additionally provides for narrower embodiments of the claimed composition, which comprise about 7.5% w/w dapsone; about 30% w/w diethylene glycol monoethyl ether; about 4% w/w acrylamide/sodium acryloyldimethyl taurate copolymer; and water (and does not comprise adapalene) (claims 2, 3, 7). Dependent claims further provide for the composition to contain methyl paraben (claims 4, 8). The claims circumscribe the treatment of any dermatological condition, including those specifically claimed (e.g., acne vulgaris, rosacea, atopic dermatitis, chronic wounds, bed sores, keratosis pilaris, sebaceous cysts, etc.), as well as other numerous and varied dermatological conditions, such as melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.

Note, for the purposes of this discussion, that the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

Dapsone was well known in the art at the time of the effective filing date as an effective treatment for acne vulgaris and rosacea. Garrett (WO 2009/108147; 2009) teaches that "[d]apsone was first synthesized in 1908 and has been used medically as an antibiotic and an anti-inflammatory" (p.11, l.4-5). Garrett teaches that both oral and topical formulations of dapsone were known in the art to be effective for the treatment of acne (p.11, l.7-8; p.11, l.31-34), and further discloses the effectiveness of topical dapsone therapy for the treatment of rosacea (abstract; p.1, l.31-35; p.3, l.5-7; p.7, l.30-p.8, l.9; Ex.1, p.23 *et seq.*). Garrett (WO 2009/061298; 2009) further teaches that 5% topical dapsone gel has been proven in clinical studies to be effective for the treatment of acne vulgaris and provides ≤1% of the systemic exposure to dapsone as that seen with typical oral dapsone therapy (p.11, l.1-4). Ahluwalia et al. (WO 2011/014627; 2011) further corroborates the efficacy of dapsone as an anti-acne compound (p.2, l.7-10). Ahluwalia et al. teaches, however, that dapsone's "mechanism of action is not entirely understood" (p.2, l.14-16). Ahluwalia et al. postulates that the anti-acne effect of dapsone is related to its effects in suppressing neutrophil recruitment and local production of toxic products, thereby "inhibiting neutrophil chemotaxis", "reducing generation of oxygen free radicals", inhibiting " release of lysosomal enzymes" and reducing " inflammatory effects of prostaglandins and leukotrienes", thereby providing an anti-inflammatory effect on acne lesions (p.2, l.16-22).

A diligent search of the prior and contemporaneous art at the time of the effective filing date of the claimed invention does not reveal any clear teachings supporting the use of dapsone for the treatment of any possible type of dermatological condition known in the art. McGeer et al. (U.S. Patent No. 5,532,219; 1996) suggests that dapsone is effective for the treatment of certain autoimmune disorders, including rheumatoid arthritis, dermatitis herpetiformis, temporal arteritis, polymyalgia rheumatic, cutaneous lupus erythematosus, Bechet's disease or polyarteritis nodosa (col.1, l.48-52), but fails to teach the usefulness of topical dapsone preparations in the treatment of any dermatological condition, including those specific conditions instantly claimed (e.g., atopic dermatitis, chronic wounds, bed sores, keratosis pilaris, nodular prurigo, sebaceous cysts, etc.), as well as any one or more of such numerous and varied dermatological conditions known in the art, such as, e.g., melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.

Applicant's claims, however, assert that the administration of the topical dapsone formulation would be effective to treat any or all such dermatological conditions known in the art (known or unknown) as of the effective filing date of the claimed invention. The concept that the skilled artisan would have been able to reasonably accomplish this objective, however, appears to fly in the face of what was known in the art at the time of the effective filing date of the claimed invention, namely that topical dapsone therapy was only recognized in the art to have clear and established efficacy in the treatment of acne vulgaris or rosacea. Moreover, Applicant's own working examples fail to demonstrate the ability of the claimed topical dapsone preparations to treat any type of dermatological condition (including those specific conditions claimed) in a patient in need thereof. Applicant's working examples are limited to specific topical preparations of dapsone and do not demonstrate the efficacy of such formulations in the treatment of any type of dermatological condition (including any or all of those specific dermatological conditions instantly claimed). There is no clear basis, then, in the proffered working examples to conclude that Applicant's claimed method of administering the recited topical dapsone preparation was capable of treating any or all types of dermatological conditions in a patient suffering from the same. As a result, the as-filed specification fails to clearly enable the full scope of embodiments circumscribed by Applicant's claimed method.

While the lack of adequate working examples cannot be the sole factor in determining enablement, the unpredictable nature of the art and the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter provide additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

As the cited art and discussion of the above factors establish, the disclosure and supporting examples provided in the present specification, coupled with the state of the art at the time of the invention, fail to imbue the skilled artisan with a reasonable expectation or ability to use the full scope of the invention as instantly claimed. In order to actually use the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. §112(a) (pre-AIA first paragraph) in order to practice the full scope of embodiments presently claimed.

Claim Rejections - 35 USC § 112(b) (Pre-AIA Second Paragraph)

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Instant Claims 1 and 7

In claims 1 and 7, the phrase "in need thereof" renders the claim indefinite because it is unclear if the patient is simply in need of the recited step of administering the topical dapsone composition (for any therapeutic purpose) or if the patient is specifically in need of treatment of "a dermatological condition". Clarification is required.

As claims 2-6 and 8-10 fail to remedy this deficiency in the claims, they are also rejected on the same grounds as instant claims 1 and 7.

Instant Claims 5 and 9

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu,* 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald,* 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall,* 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche,* 86 USPQ 481 (Bd. App. 1949).

In claims 5 and 9, Applicant recites various examples of broader species of dermatological conditions that contain within their scope other species listed in the Markush group. For example, "dermatitis" is generic to "atopic dermatitis" or "eczema" (Benhamou et al., U.S. Patent Application Publication No. 2012/0064144, March 2012, teaches that eczema is a form of dermatitis; p.1, para.[0003]). Also, claims 5 and 9 recite "inflammatory dermatoses", which is also generic to the species of "atopic dermatitis" or "eczema", as the term "dermatitis" necessarily implies the presence of inflammation (Santa, U.S. Patent No. 5,989,571; col.1, l.50-51). Still further, claims 5 and 9 recite "chronic wounds", which is generic to the species of "bed sores". The use of such conflicting broad and narrow limitations in the same claim renders the claim unclear as to which types of dermatological conditions are permitted within the Markush group and which are not.

For example, contact dermatitis is a type of dermatitis, which suggests that it might be included within the Markush group; however, the Markush group lists other specific types of dermatitis that are not contact dermatitis, indicating that contact dermatitis is not actually within the claimed Markush group. Similarly, seborrheic dermatitis is a type of dermatitis, which suggests that it would be included in the Markush group, but the Markush group lists specific species of dermatitis (i.e., atopic dermatitis) that are not seborrheic dermatitis, which again implies that this species is not actually within the Markush group claimed. Clarification is required.

In claims 5 and 9, the intended distinction between "dermatitis" and "inflammatory dermatoses" is not clearly set forth in the claim. Santa (U.S. Patent No. 5,989,571; col.1, l.50-51) teaches that the term "dermatitis" is necessarily characterized by inflammation (thus, constituting "inflammatory dermatoses"). Either the recitation of both "dermatitis" and "inflammatory dermatoses" is redundant or it defines different conditions that are not clearly distinguished by the claim. Clarification is required.

In claims 5 and 9, the phrase "treatment of chronic wounds" renders the claim indefinite because it is unclear if the "dermatological condition" to be treated is "chronic wounds" *per se* or some other unspecified aspect of "treatment of chronic wounds". Clarification is required.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112(b) (pre-AIA second paragraph) and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009) in view of Hani et al. (WO 2010/105052 A1; 2010).

Garrett teaches dapsone compositions with a pharmaceutically acceptable carrier for topical delivery of dapsone (p.12, l.1-2).

Garrett teaches that the topical composition preferably includes a thickening agent or thickener as part of the carrier, such as, e.g., polymeric thickeners, to increase viscosity, stability and improve suspending capability when added to a mixture (p.13, l.22-29). Garrett discloses polymeric thickeners that may be employed in the composition, such as the gelling agent CARBOPOL, a cross-linked acrylic acid polymer (also known as carbomer), and further teaches that the thickener generally comprises between about 0.2-4% w/w of the composition (p.15, l.5-19).

Garrett additionally teaches that the topical composition includes an organic solvent system, preferably diethylene glycol monoethyl ether (DGME, also known as ethoxydiglycol; p.13, l.30-p.14, l.2), which is generally incorporated in an amount of about 25-35% w/w of the composition (p.17, l.4-12).

Garrett teaches that the topical composition also preferably contains a preservative to prevent or diminish microorganism growth, such as methyl paraben (p.17, l.14-21).

Garrett further discloses that the topical composition comprise between 0.5-10% w/w dapsone (p.19, l.24-25).

Garrett teaches a preferred composition comprising about 5% w/w dapsone; about 0.85% w/w carbomer 980; about 25% w/w DGME; about 0.2% w/w methyl paraben; about 0.2% w/w sodium hydroxide; and about 68.75% w/w purified water (p.20, l.6-9).

Garrett teaches that the relative percentages of each of the components of the composition may be varied depending upon the desired strength of the formulation, gel viscosity, and desired ratio of microparticulate to dissolved dapsone (p.20, l.10-13).

Garrett further teaches that the compositions are effective for the treatment of rosacea by applying the dapsone composition once or twice daily (p.3, l.5-6; p.7, l.30-p.8, l.9).

Garrett differs from the instant claims only insofar as it does not explicitly teach (1) acrylamide/sodium acryloyldimethyl taurate copolymer in an amount of "about 2% to about 6% w/w" (claim 1), particularly about 4% w/w (claim 7) or (2) the exact claimed amount of DGME (i.e., “about 30% w/w”; claims 2, 7) or the exact claimed amount of dapsone ("about 7.5% w/w"; claims 1 and 7).

Hani et al. teaches that acrylamide/sodium acryloyldimethyl taurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p.24-28, para.[0118]; abstract).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting the cross-linked acrylic acid polymer (also known as carbomer or CARBOPOL) thickener of the dapsone formulation described in Garrett as being advantageously incorporated in an amount of 0.2-4% w/w (which clearly suggests amounts of "about 4% w/w" as claimed) with acrylamide/sodium acryloyldimethyl taurate copolymer because each was well

known in the art to be a suitable thickening agent for topical personal care products, as evidenced by Garrett and Hani et al. The substitution, therefore, of one for the other would have been *prima facie* obvious before the effective filing date of the claimed invention because the cross-linked acrylic acid polymer and acrylamide/sodium acryloyldimethyl taurate copolymer were known functional equivalents in the topical pharmaceutical art. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

In further support of *prima facie* obviousness, note that the teachings in Garrett provide for ranges of dapsone, DGME and polymeric thickener that clearly meet and/or circumscribe the ranges instantly claimed. See, e.g., Garrett at p.15, l.5-19; p.17, l.4-12; and p.19, l.24-25, which disclose the use of 0.5-10% w/w dapsone and about 25-35% w/w DGME, as well as about 0.2-4% w/w polymeric thickener (which clearly suggests the use of the same amount of another thickener, such as that of Hani et al.). Such ranges clearly overlap or encompass Applicant's instantly claimed amounts of:

(i) "about 7.5% w/w" dapsone (claims 1 and 7);

(ii) "about 30% w/w" DGME (claims 2 and 7); and

(iii) "about 2% w/w to about 6% w/w" polymeric thickener (claim 1), particularly "about 4% w/w" (claims 3 and 7).

Note, further, that Garrett clearly suggests the incorporation of a polymeric thickener in an amount of about 0.2-4% w/w of the composition, which clearly suggests the incorporation of another thickener, such as the acrylamide copolymer thickener of Hani et al., within such a desirable range. The disclosure of incorporating the polymeric thickener within the range of 0.2-4% w/w of the composition is a clear suggestion to incorporate the polymeric thickener (such as that of Hani et al.) in an amount that constitutes "about 4% w/w" of the composition as instantly claimed (claims 1, 3 and 7).

Thus, Garrett teaches the use of such components in amounts that clearly meet or encompass the ranges specifically recited in the present claims. As stated by the MPEP at §2144.05, "In the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)..."[A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in varying the amounts of the components of the composition described in Garrett within the disclosed ranges therein. This is because Garrett teaches that the components may be employed in varying amounts within the described parameters, while retaining the therapeutic functionality of the composition. The selection of the optimal amounts of the components of the composition would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the individual components may be varied within the broader ranges described in Garrett while still preserving the therapeutic properties of the composition. Moreover, the fact that the claimed ranges overlap and fall within those described in the prior art is clear evidence of *prima facie* obviousness. MPEP §2144.05.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention.

Claims 6 and 10 are rejected under 35 U.S.C. 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009) in view of Hani et al. (WO 2010/105052 A1; 2010), as applied above to claims 1-5 and 7-9, taken in further view of Garrett (WO 2009/061298; 2009).

Garrett '147 in view of Hani et al. as applied above to claims 1-5 and 7-9.

Garrett '147 in view of Hani et al. differ from the instant claims only insofar as they do not explicitly teach administration of the topical dapsone preparation to treat acne vulgaris (claims 6, 10).

Garrett '298 teaches that oral dapsone was known to be effective for the treatment of acne (p.9, l.31-34). Garrett '298 teaches that topical dapsone gel formulations have been shown to be effective in the treatment of acne vulgaris and result in ≤1% of the systemic exposure that is seen with typical oral dapsone treatment (p.11, l.1-4).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the topical dapsone preparation of Garrett '147 in view of Hani et al. for the treatment of acne vulgaris because Garrett '298 teaches that topical dapsone was known in the art to be an effective treatment for acne vulgaris. The skilled artisan would have been motivated to do so because dapsone was well known in the art to be an effective therapy for treating acne vulgaris and topical application of dapsone for this purpose was known to significantly reduce systemic exposure to dapsone as compared to oral therapy, thereby reducing adverse side effects associated with dapsone therapy for acne. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan before the effective filing date of the claimed invention to employ the topical dapsone preparation of Garrett '147 in view of Hani et al. for the purpose of treating acne vulgaris.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art before the effective filing date of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that

meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9,161,926.

'926 claims a topical pharmaceutical composition comprising about 7.5% w/w dapsone, about 30% w/w to about 40% w/w diethylene glycol monoethyl ether, about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer, and water, wherein the composition does not comprise adapalene (patent claims 1-3). '926 additionally claims an embodiment of this topical pharmaceutical composition that comprises about 7.5% w/w dapsone, about 30% w/w diethylene glycol monoethyl ether, about 4% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer, and water, also wherein the composition does not comprise adapalene (patent claim 5). '926 additionally provides for the topical composition to further comprise methyl paraben (patent claims 4, 6).

'926 differs from the instant claims only insofar as it does not explicitly claim a method for treating a dermatological condition, e.g., acne vulgaris, by administering the claimed topical composition (claims 1, 5-7, 9-10).

In the '926 disclosure, however, the patentee discloses that the topical dapsone composition is therapeutically effective for the treatment of various dermatological conditions, including acne vulgaris, rosacea, atopic dermatitis, bed sores, keratosis pilaris, etc. (col.3, l.28-45; col.11, l.60-col.12, l.10).

A person of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in administering the topical dapsone composition as provided for in the '926 claims to a subject in need of treatment of the recited dermatological conditions for the purpose of treating the same because the '926 disclosure specifically teaches that the topical dapsone composition may be formulated for the purposes of treating the same dermatological conditions as instantly claimed. The skilled artisan would have sought to employ the topical dapsone composition of the '926 claims for the additional therapeutic utilities disclosed in the specification of the '926 patent for medicinal purposes. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan at the time of the instant invention to utilize the topical dapsone composition of the '926 claims for the treatment of the same

dermatological conditions as instantly claimed in view of the utilities disclosed by the patentee of the '926 claims.

A patent's "disclosure may be used...to answer the question whether claims merely define an obvious variation of what is earlier disclosed and claimed." *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust,* 112 USPQ2d 1001, 1012 (Fed. Cir. 2014) (quoting *In re Basell Poliolefine Italia S.P.A.,* 89 USPQ2d 1030, 1036 (Fed. Cir. 2008). The '926 patent discloses that the above-cited utilities are within the scope of the invention. These aspects of the instant claims are, therefore, obvious over the '926 patent. The *AbbVie* court explicitly noted that the Federal Circuit has "repeatedly approved examination of the disclosed utility of the invention claimed in an earlier patent to address the question of obviousness" and that "a later expiring patent is not patentably distinct from an earlier expiring patent if it merely claims a disclosed utility of the earlier claimed invention." *Id.* For example, when the claims in a later-expiring patent "merely recite methods of administering" the compositions claimed in the earlier patent, they are not patentably distinct over the claims of the earlier expiring patent." *Id.* (quoting *Pfizer, Inc. v. Teva Pharms. USA, Inc.,* 86 USPQ2d 1001, 1008 (Fed. Cir. 2008)).

This is a non-provisional nonstatutory double patenting rejection.

Claims 1-5 and 7-9 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8,586,010, or are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani et al. (WO 2010/105052 A1; 2010).

'010 or '841 each individually claim a method of treating rosacea in a patient in need thereof by administering a topical dapsone preparation that comprises about 5 wt% dapsone, about 0.85 wt% carbomer 980, about 25 wt% diethylene glycol monoethyl ether, about 0.2 wt% methyl paraben, about 0.2 wt% sodium hydroxide and about 68.75 wt% purified water.

The amounts of dapsone ("about 5 wt%") or diethylene glycol monoethyl ether ("about 25 wt%") as recited in the '010 or '841 claims are understood to meet Applicant's required amounts of "about 7.5%

w/w" dapsone and "about 30% w/w" diethylene glycol monoethyl ether as provided for in instant claims 1, 2 and 7, absent any explicit definition of the amount of variation tolerated by the term "about" as used in the instant claims.

'010 or '841 differ from the instant claims only insofar as they do not explicitly teach the incorporation of acrylamide/sodium acryloyldimethyl taurate copolymer in an amount of "about 4% w/w" (claims 1, 3, 7).

Garrett teaches dapsone compositions with a pharmaceutically acceptable carrier for topical delivery of dapsone (p.12, l.1-2). Garrett teaches that the topical composition preferably includes a thickening agent or thickener as part of the carrier, such as, e.g., polymeric thickeners, to increase viscosity, stability and improve suspending capability when added to a mixture (p.13, l.22-29). Garrett discloses polymeric thickeners that may be employed in the composition, such as the gelling agent CARBOPOL, a cross-linked acrylic acid polymer (also known as carbomer), and further teaches that the thickener generally comprises between about 0.2-4% w/w of the composition (p.15, l.5-19). Garrett further teaches that the compositions are effective for the treatment of rosacea by applying the dapsone composition once or twice daily (p.3, l.5-6; p.7, l.30-p.8, l.9).

Hani et al. teaches that acrylamide/sodium acryloyldimethyl taurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p.24-28, para.[0118]; abstract).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting carbomer thickener of the dapsone formulation of the '010 or '841 claims with acrylamide/sodium acryloyldimethyl taurate copolymer because each was well known in the art to be a suitable thickening agent for topical personal care products, as evidenced by Garrett and Hani et al. The substitution, therefore, of one for the other would have been *prima facie* obvious before the effective filing date of the claimed invention because the cross-linked acrylic acid polymer and acrylamide/sodium acryloyldimethyl taurate copolymer were known functional equivalents in the topical pharmaceutical art. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect

from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-1396, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1982) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

The skilled artisan also would have had a reasonable expectation of success in incorporating the acrylamide copolymer thickening agent into the topical dapsone preparation in an amount of, e.g., "about 4% w/w" as instantly claimed because Garrett teaches topical dapsone formulations for the treatment of rosacea in which the polymeric thickening agent is included in amounts of up to 4% w/w of the composition. The skilled artisan would have recognized that the optimal amount of the polymeric thickening agent would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the polymeric thickener may be advantageously included in topical dapsone formulations in an amount of up to 4% w/w of the composition and still constitute a therapeutically effective preparation for the treatment of rosacea, as evidenced by Garrett.

This is a non-provisional rejection over the claims of U.S. Patent No. 8,586,010 and a provisional rejection over the claims of U.S. Patent Application No. 14/063,841.

Claims 6 and 10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8,586,010, or are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani et al. (WO 2010/105052 A1; 2010) as applied above to claims 1-5 and 7-9, further in view of Garrett (WO 2009/061298; 2009).

'010 or '841 as applied above to claims 1-5 and 7-9, each alternatively taken in view of Garrett '147 and Hani et al.

'010 or '841, each alternatively taken in view of Garrett '147 and Hani et al., differ from the instant claims only insofar as they do not explicitly teach administration of the topical dapsone preparation to treat acne vulgaris (claims 6, 10).

Garrett '298 teaches that oral dapsone was known to be effective for the treatment of acne (p.9, l.31-34). Garrett '298 teaches that topical dapsone gel formulations have been shown to be effective in the treatment of acne vulgaris and result in ≤1% of the systemic exposure that is seen with typical oral dapsone treatment (p.11, l.1-4).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the topical dapsone preparation of the '010 or the '841 claims, each alternatively taken in view of Garrett '147 and Hani et al., for the treatment of acne vulgaris because Garrett '298 teaches that topical dapsone was known in the art to be an effective treatment for acne vulgaris. The skilled artisan would have been motivated to do so because dapsone was well known in the art to be an effective therapy for the treatment of acne vulgaris and topical application of dapsone for this purpose was known to significantly reduce systemic exposure to dapsone as compared to oral therapy, thereby reducing the adverse side effects associated with dapsone therapy for acne. It would, therefore, have been *prima facie* obvious to the ordinarily skilled artisan before the effective filing date of the claimed invention to employ the topical dapsone preparation of the '010 or '841 as modified by Garrett '147 and Hani et al. for the purpose of treating acne vulgaris.

This is a non-provisional rejection over the claims of U.S. Patent No. 8,586,010 and a provisional rejection over the claims of U.S. Patent Application No. 14/063,841.

Conclusion

Rejection of claims 1-10 is proper.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

November 12, 2015

Notice of References Cited	Application/Control No. 14/885,805	Applicant(s)/Patent Under Reexamination WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	Page 1 of 1

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	G	US-				
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	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

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	N	WO 2009/061298 A1	05-2009	WO	Garrett	-
	O	WO 2009/108147 A1	09-2009	WO	Garrett	-
	P	WO 2010/105052 A1	09-2010	WO	Hani et al.	-
	Q	WO 2011/014627 A1	02-2011	WO	Ahluwalia et al.	-
	R					
	S					
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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
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	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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(54) Title: TOPICAL PERSONAL CARE AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

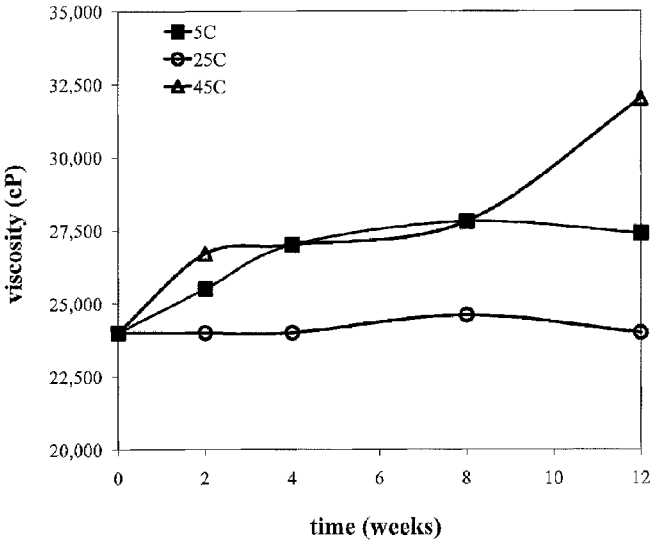

Fig: 1

(57) Abstract: Topical compositions are provided that have 0.5% or more of at least one personal care or pharmaceutical acid, and lightly- to moderately-crosslinked PVP, which is an effective thickener in the low pH systems. In preferred embodiments, the acid is a hydroxy acid and the composition used for personal care, or prescriptive or non-prescriptive medication indications for use on the skin, hair, scalp, foot, or lips. Also provided is the use of the topical compositions to deliver the acid(s) to the skin, hair, scalp, foot, or lips. Especially preferred is a use to reduce irritation and stinging compared to an equivalent compositions not having lightly- to moderately-crosslinked PVP.

WO 2010/105052 A1

TOPICAL PERSONAL CARE AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to topical compositions comprising at least one personal care acid or one pharmaceutical acid, and lightly- to moderately crosslinked poly(*N*-vinyl-2-pyrrolidone) ("PVP"). The lightly- to moderately crosslinked PVP has been found to provide unique thickening effects in acidic systems that are essentially stable (*e.g.*, do not phase separate and maintain rheological properties) even with prolonged storage.

[0002] Particularly, the invention relates to the compositions having 0.5% (% w/w) or more of at least one personal care acid or pharmaceutical acid. These compositions ideally have an acidic pH, especially a pH less than 6, and more preferably a pH less than 4, and especially preferably less than 2. These formulations find application on the skin, hair, scalp, foot, or lip of an mammal, preferably man, as a smoothing composition, a moisturizing composition, a skin firming composition, a skin lightening composition, an age-spot composition, a shampoo, or a cream for use around the eyes or mouth.

[0003] Surprisingly, the topical compositions described herein deliver the personal care and/or pharmaceutical acid with reduced skin irritation, a significant breakthrough in this field where discomfort issues are well known.

DESCRIPTION OF RELATED ART

[0004] Topical personal care and pharmaceutical compositions are products consumers around the globe have come to depend and rely on for the innumerable benefits they impart. Sold both by prescription and over-the-counter (non-prescriptive), they are applied to the exterior of the body to the skin, scalp, hair, feet, and lips. They may be cosmetic in effect, meaning they impart primarily aesthetically beneficial results (like minimizing fine lines and wrinkles), or they may relieve or cure clinical conditions (like acne vulgaris or warts), or fall somewhere between the cosmetic and medical indications. Across all these uses, many different product forms are employed, and vary

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from thickened "semi-solids" like foundations, concealers, lipsticks, and lip balms, to creamy emulsions, gels, ointments, and lotions, or may be lighter "bodied" compositions such as liquid soaps, washes, and rinses. In short, topical personal care and pharmaceutical compositions are ubiquitous in today's modern world.

[0005] It has been known for some time that acidic personal and pharmaceutical compositions elicit special responses when applied topically. In this broad concept, the term *low pH* means having a pH of 6 or less. More particularly, low pH compositions can cause an increase in epidermis exfoliation to alleviate skin conditions (*e.g.*, hyperkeratosis, dry/flaky/itchy skin), enhance moisturization to help minimize the appearance of lines and wrinkles, increase dermal thickness, and increase dermal perfusion (vascular effects). A review of these actions as related to a particular type of acids, hydroxy acids and retinoids, is provided in Ramos-e-Silva, *et al.*, "Hydroxy acids and retinoids in cosmetics," *Clinics in Dermatog.*, 2001; 19:460-466, which is hereby incorporated in its entirety by reference. Also, an instructive review of alpha hydroxy acids, including the types, mechanisms of action, formulations, and treatment results, is provided by Van Scott, E.J., "Alpha-hydroxyacids in the treatment of signs of photoaging," *Clinics in Dermat.*, 1996; 14: 217-226, which also is incorporated in its entirety by reference. This article recognizes pHs in the range from 0.6 to 4.0.

[0006] While low pH topical compositions can provide useful benefits to the consumer, they can pose real challenges to the formulation scientist, production staff, and even the consumer. It is well appreciated by one skilled in the art that low pH fluids can be difficult to thicken, or to maintain a stable viscosity and/or pH. Thickeners commonly used in low pH systems include xanthan gum and magnesium aluminum silicate combinations. At addition levels to create "thick" or "stiff" consistencies, these thickeners may cause pilling (localized formulary incompatibility that leads to coagulation) or impart an unpleasant, stringy texture to the end product.

[0007] Alternatively, acrylic acid polymers, and polyacrylamides may be used. Their manufacturers usually recommend dispersing them in water and then neutralizing to attain a desired viscosity target, which simply is not possible when the product inherently remains strongly acidic.

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[0008] Other thickeners are known. For example, Carbopol® Aqua SF-1, a lightly crosslinked acrylate copolymer is sold by The Lubrizol Corporation. Product information indicates it is effective at a pH of 3.5 and higher. Also sold by The Lubrizol Corporate is Carbopol® Aqua CC Polymer, a polyacrylate-1 crosspolymer. The product white paper recommends neutralizing the polymer between a pH of 3.5 to 4.0, and, optionally, the pH can be adjusted (higher) by the addition of base. However, there still remains a need for a thickening agent that is effective at pHs of 6 or less, more preferably at very low pHs of 4 or less, and especially at extremely low pH of 2 or less.

[0009] Also known is U.S. patent 5,422,112, which discloses a thickener system including a combination of xanthan gum, magnesium aluminum silicate and polyacrylamide. The compositions are the to be particularly effective at low pH used especially for thickening alpha-hydroxy carboxylic acids and salts thereof. Typically, magnesium aluminum silicates have a recommended pH range of about 4.2 to 5.2, and typically are not the choice thickener for very low pH systems.

[0010] Similarly, U.S. patent 5,874,095 claims an enhanced skin penetration system comprising a nonionic polyacrylamide of high molecular weight, for improved topical delivery of drugs at low pH.

[0011] Further descriptions of acrylic acid thickeners are given in U.S. patents 2,883,351; 2,956,046; 3,035,004; and 3,436,378.

[0012] Poly(*N*-vinyl-2-pyrrolidone) and its salts and esters are described in U.S. patents 6,436,380; 6,197,281; 6,333,039; 6,685,952; and 7,108,860 as rheology modifiers or thickeners in personal care products.

[0013] U.S patent application 2003/0118620 teaches a thickening system for cosmetic composition of low pH, comprising a polysaccharide and taurate copolymer.

[0014] Polymeric thickeners for acidic surfactant compositions are described by U.S. patent 4,552,685, and by U.S. patent 4,529,773. However, these acidic-thickened solutions require high levels of surfactant in order to solubilize the copolymers and they have higher viscosities at pH 7 than when the pH is lowered into the acidic region.

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[0015] As shown in this summary, there remains a strong demand and need for a thickening material for low pH, very low pH, and extremely low pH systems, particularly one that maintains stable viscosity, pH, and preferably viscosity and pH. Preferably, this thickener is easy to handle, readily dispersible, and provides smooth, thickened consistencies, without being stringy or creating pilling.

[0016] Interest in thickening acidic compositions stems, in part, from the growth of acid products that consumers are demanding and using. Although the use of alpha hydroxy acids as therapy for photoaged skin was known to medical doctors by 1989 (Van Scott, E.J., "Alpha hydroxy acids: procedures for use in clinical practice, *Cutis*, 1989; 43: 222-228), a non-prescriptive market demand did not exist until 1992, when Avon launched *Anew Perfecting Complex For Face* (Avon Products, Inc. website: www.avoncompany.com/brands/skincare.html). Indeed, the U.S. Food and Drug Administration (FDA) confirms that it was not until 1992 that they received the first four registrations for new consumer products containing glycolic acid as an active ingredient (Barrows, J.N., Memorandum to the Administrative File, "Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients," Office of Cosmetics and Colors, CFSAN, FDA, September 12, 2002.) Market demand for these low pH, topically applied products grew such that by 1997 forty-two such product registrations were received by the FDA.

[0017] With the growth of this new market segment, consumers began to experience potentially harmful side effects like stinging, redness, and burning. Between 1992 and 2004 the FDA received 114 side-effect complaints (U.S. Food and Drug Administration, *Guidance: Labeling for cosmetics containing alpha hydroxy acids*, http://www.cfsan/fda/gov/guidance.html, January 10, 2005). Hence, there remains a real need for products and methods for reducing the irritation of these products while maintaining their efficacy in treating various skin and hair conditions.

[0018] As it will be explained later, the present invention is also related to lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone). This polymer was first introduced in U.S. patent 5,073,614. In that patent it is taught to be the precipitation polymerization product of *N*–vinyl-2-

pyrrolidone monomer in an organic solvent, such as an aliphatic hydrocarbon solvent (preferably cyclohexane or heptane) or an aromatic hydrocarbon (such as toluene) in the presence of about 0.2% to 1% by weight of a crosslinking agent. The fine, white powders thus produced have an aqueous gel volume of about 15 mL to 150 mL of polymer, and a Brookfield viscosity in 5% aqueous solution of at least about 10,000 cP.

[0019] This lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer also was the subject of U.S. patent 5,139,770, filed December 17, 1990 and issued August 18, 1992. In this patent examples are provided for a cream rise (pH of 4), a hair conditioner (pH of 4), and a blow dry styling lotion (pH of 6), which have been pH-adjusted by the addition of citric acid or phosphoric acid. Although not specified, one skilled in the art recognizes that the acid addition level in these formulations is small, much less than 0.5% (% w/w). As such, formulation scientists regard these acids at these levels not as *functional* acids (*e.g.*, for the *treatment* of skin or hair conditions), but, instead as *pH adjustors*, necessary to protonate the quaternary polymer(s) to make them more substantive to hair.

[0020] U.S. patent 5,716,634 teaches a lightly-crosslinked *N*-vinyl lactam polymer in form of stable, clear, flowable, homogenized hydrogel, may be used as a carrier for cosmetic/pharma active for hair or skin use. A controlled release drug-delivery composition comprising a lightly-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer is the subject of U.S. patent 5,252,611. Also, the production of lightly-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer in an oil-in-water or water-in-oil emulsion is taught in U.S. patent 6,177,068.

[0021] A summary of some properties of light- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) is given in Shih, J.S., "Characteristics of lightly crosslinked poly(N-vinylpyrrolidone)," *Polymer Materials: Science & Engineering Preprint*, 72, 374, 1995.

[0022] Still more information on this lightly crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer is given in the following U.S. patents: 5,162,417; 5,312,619; 5,622,168; 5,564,385; and 6,582,711.

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[0023] These nine U.S. patents ('770, '634, '611, '068, '417, '619, '168, '385, and '711) and the Shih article mentioned in the above paragraphs are hereby incorporated in their entirety by reference.

[0024] Hence, a first objective of the present invention is to provide a wide range of easy-to-use, topical compositions having at least one personal care or pharmaceutical acid that are effectively thickened. The invention also seeks a method to deliver the personal care/pharmaceutical acid(s), and also the use of this method to reduce the perceived irritation and sting discomfort so these compositions find greater efficacy and consumer appeal.

SUMMARY OF THE INVENTION

[0025] Surprisingly, it has been discovered that lightly- to moderately-crosslinked PVP effectively and quite elegantly thickens topical compositions having a personal care or pharmaceutical acid, even at a low pH of 6 or less, or very low pHs of 4 or less, or even extremely low pHs of 2 or less.

[0026] Additionally and even more surprising, it has been discovered that the use of these topical compositions thickened with lightly- to moderately-crosslinked PVP reduce irritation and sting discomfort compared to formulas without the lightly- to moderately-crosslinked PVP.

[0027] Hence, a first object of the present invention is to provide a thickener system particularly suited for use with acidic topical compositions, wherein the thickening agent comprises lightly- to moderately-crosslinked PVP. The topical compositions are those compositions for use on the exterior (*i.e.*, skin, hair, feet, and/or lips) of an mammal, such as man, horses, cats, and dogs. These thickened compositions serve both prescriptive and non-prescriptive markets, such as pharmaceutical and personal care compositions for skin care, hair care, foot care, scalp care, and sun care.

[0028] In these topical compositions the amount of lightly- to moderately-crosslinked PVP represents from about 0.5% to about 10% by weight of the total composition, and more preferably from about 1% to about 6% by weight. At these addition levels the low-shear ("Brookfield") viscosity typically is about 7000 cP or more, and more typically is about 10,000 cP or more.

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[0029] A second objective of the present invention is the use of these thickened, acidic compositions to deliver the personal care and/or pharmaceutical acid to the exterior of a mammal, and to use this method to reduce irritation and sting compared to compositions not having the lightly- to moderately-crosslinked PVP.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] Figure 1 is a graph of viscosity as a function of time for an acne gel produced in accordance with Example 8.

[0031] Figure 2 is a graph of pH as a function of time for an acne gel produced in accordance with Example 8.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

[0032] The present invention relates to compositions comprising at least one personal care or pharmaceutical acid, and lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) ("lightly- to moderately-crosslinked PVP") to thicken the composition. Surprisingly, it has been discovered that the lightly- to moderately-crosslinked PVP increases the viscosity of these compositions, stabilizing the viscosity and pH of these formulations that historically have proved difficult to thicken and stabilize. Lightly- to moderately-crosslinked PVP creates elegant, smooth, thickened compositions even at a pH as low as 1.3, a performance that is essentially unmatched by other thickeners.

[0033] Additionally, the invention relates to the use of these thickened compositions to deliver the acid to the skin, scalp, feet, or lips of a mammal, preferably man. Even more surprising, it has been discovered that the use of such thickened acidic compositions reduce irritation and sting discomfort compared to an equivalent formulation not having the lightly- to moderately-crosslinked PVP.

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[0034] Due to the inherent complexity in these compositions, their ingredients, product forms, and uses, it will be appreciated that definitions of terms will help describe preferred embodiments of the invention.

[0035] The term *personal care compositions* (or *formulations*) refer to compositions intended for topical use on a mammal, including, man, horses, cats, and dogs. These compositions include skin, hair, scalp, foot, or lip compositions, including those compositions that can be purchased with and without a doctor's prescription. These personal care compositions can provide any number of known benefits, such as: moisturize, prevent wrinkles, treat wrinkles, firm skin, treat blemishes, protect from ultraviolet radiation, protect from thermal damage, lighten skin color, remove dirt / soil / dead skin / blocked pores, and treat keratosis (*e.g.*, corns, calluses, and warts). The personal care compositions also may comprise other active and non-active ingredients to assist in their benefit, delivery, spreadability, emolliency, film formation, stability, and/or thickening.

[0036] The term *lightly- to moderately-crosslinked PVP*, unless otherwise noted, specifically refers to polymer essentially consisting of lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) having at least one of the following characteristics: (1) an aqueous swelling parameter defined by its gel volume from about 15 mL/g to about 300 mL/g, more preferably from about 15 mL/g to about 250 mL/g, and most preferably from about 15 mL/g to about 150 mL/g, or (2) a Brookfield viscosity of 5% lightly- to moderately-crosslinked PVP in a liquid carrier comprising water at 25°C of at least 2,000 cP, more preferably of at least about 5,000 cP, and most preferably of at least about 10,000 cP. Disclosure for these parameter ranges is provided in U.S. patent 5,073,614 and in Shih, J.S., *et al.* (1995). Synthesis methods for the lightly- to moderately-crosslinked PVP are disclosed in a number of references, including U.S. patents 5,073,614; 5,654,385; and 6,177,068. It is appreciated by a polymer scientist skilled in the art that the method of synthesis is immaterial, inasmuch as the produced polymer achieves at least one of the abovedefined parameters.

[0037] For example, U.S. patent '614 discloses different crosslinkers and crosslinker amounts that yield lightly- to moderately-crosslinked PVP suitable for the present invention. The effect of crosslinker amount on swell volume and viscosity is graphically presented in Shih, J.S., *et al.* (1995). Thus, the lightly- to moderately-crosslinked PVP may be produced by the precipitation

polymerization method of the '614 patent, by the hydrogel method described in the '385 patent, or by the non-aqueous, heterogeneous polymerization method of the '068 patent. Certainly, other techniques are contemplated to synthesize this polymer, provided the product meets the aqueous swelling parameter and Brookfield viscosity requirements.

[0038] Final product viscosities may slightly vary for compositions containing lightly- to moderately-crosslinked PVP made by these different methods. Nonetheless, these variations are within the scope of the invention, as the lightly- to moderately-crosslinked PVPs thicken low pH compositions.

[0039] Unless otherwise specified, "lightly- to moderately-crosslinked PVP" does not refer to swellable but water-insoluble crosslinked PVP, such as the type sold into commercial trade under the trade name Polyclar® by International Specialty Products, which differs from the abovedescribed lightly- to moderately-crosslinked PVP.

[0040] The term *viscosity* refers to the proportionality coefficient between shear stress and shear rate, and describes a composition's resistance to flow. Because viscosity is dependent on shear rate, specific measurement information (such as viscometer, flow apparatus/spindle, and shear rate) is required to properly define viscosity. As used herein, *viscosity* refers to the proportionality coefficient determined from low shear rate, rotational flow, especially the viscosity measured by the Brookfield LVT and Brookfield RVT viscometers operating at 10 revolutions per minute (rpm) at 25°C. References describing the Brookfield measurement of viscosities include the following, each of which is hereby incorporated in its entirety by reference: Thibodeau, L., "Measuring viscosity of pastes," *American Laboratory News*, June 2004; McGregor, R.G., "Shelf life: does viscosity matter?" *Pharmaceutical Online*, October 31, 2007; and McGregor, R.G., "When ointments disappoint, the viscosity story," Brookfield Engineering brochure.

[0041] The term *sub-formulation* refers to a composition having two or more ingredients that is first prepared and then later blended with other ingredients as necessary. For example, sub-formulations may be made containing thickening agent(s) and liquid carrier(s) [which may or may not be solvents for the thickening agent(s)] with or without additional ingredients, and then divided into specific lots for use in specific formulation(s) at a later time.

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[0042] The term *topical* refers to any external parts of a mammal, such as man, horses, cats, and dogs, and especially man, and includes skin, hair, scalp, lips, and feet.

[0043] The term *low pH* refers to a pH of 6 or less.

[0044] The term *very low pH* refers to a pH of 4 or less.

[0045] The term *extremely low pH* refers to a pH of 2 or less.

First embodiment of the invention

[0046] In a first embodiment of the invention, topical compositions are provided that have at least one personal care acid or at least one pharmaceutical acid, and lightly- to moderately-crosslinked PVP. In these compositions the lightly- to moderately-crosslinked PVP functions, in part, as a thickener, especially to increase the low shear viscosity. It is surprising that lightly- to moderately-crosslinked PVP effectively thickens low pH, very low pH, and extremely low pH personal care and pharmaceutical compositions, with results that are essentially unmatched by existing thickeners.

[0047] By virtue of having at least one personal care or pharmaceutical acid, these topical compositions have a pH of less than 7, and more preferably, are low pH compositions. Even more preferable, these compositions have a very low pH, and in especially preferred embodiments, these compositions have an extremely low pH. Generally speaking, very low pH and extremely low pH are of greatest interest to the invention, as these compositions have proved most problematic to thicken. As it will be discussed in greater detail separately, the use of acidic topical compositions thickened with lightly- to moderately-crosslinked PVP has been discovered to produce less skin irritation and sting than identical formulations without lightly- to moderately-crosslinked PVP.

[0048] A broad selection of personal care acid and pharmaceutical acid compositions may be successfully thickened according to the invention. Generally speaking, a most preferred family is the hydroxy acid family, as their formulations most frequently exhibit acidic pHs that are difficult to thicken and stabilize. Hydroxy acids can be divided into four subfamilies: alpha hydroxy acids,

beta hydroxy acids, alpha and beta hydroxy acids, and polyhydroxy acids.

[0049] Alpha hydroxy acids are frequently employed in skin lotions and the like, as they are among the most useful exfoliation agents. By definition, alpha hydroxy acids possess a carboxylic acid group with a hydroxyl group on the adjacent carbon atom. Both naturally occurring and synthetic alpha hydroxy acids are known and suitable for use in the invention. Examples of alpha hydroxy acids include, without limitation: alpha hydroxyethanoic acid, alpha hydroxyoctanoic acid, alpha hydroxycaprylic acid, ascorbic acid, adipic acid, caprylic acid, capric acid, glycolic acid, lactic acid, lauric acid, mandelic acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, ricinoleic acid, oleic acid, tartaric acid, elaidic acid, and erucic acid.

[0050] Most preferred are alpha hydroxy acids that exhibit high epidermis penetration so that they may exert a maximum effect on the underlying dermis layer. Thus, the most effective alpha hydroxy acids are those of small molecular weight, such as glycolic acid and lactic acid. This preference, however, is not to say that the invention does not work in thickening higher molecular weight acids. Rather, this preference merely recognizes a special class of hydroxy acids that are used in many personal care and pharmaceutical compositions.

[0051] Like their alpha counterparts, beta hydroxy acids also find utility in the invention and in skin care products due to their ability to penetrate the epidermis and activity in the dermal layer. Beta hydroxy acids are those molecules having a carboxylic acid group and a hydroxyl group separated by two carbon atoms. Again, both naturally occurring and synthetic beta hydroxy acids are known and may be used in the invention's compositions. Specific examples of beta hydroxy acids include, but are not limited to: beta hydroxybutanoic acid, tropic acid, trethocanic acid, salicylic acid, and 5-(*n*-octanoyl) salicylic acid.

[0052] Also for use in the thickened topical compositions are alpha beta hydroxy acids. As the same suggests, these acids contain at least one alpha hydroxy acid group and one beta hydroxy acid group. Examples of alpha beta hydroxy acids include: malic acid, citric acid, and tartaric acid.

[0053] A final member of the hydroxy acid family is the polyhydroxy acid, which, as the name suggests, are molecules having at least one carboxylic acid functional group and more than 1

hydroxyl group. Polyhydroxy acids also may be naturally occurring or synthetically manufacturered, and have a higher molecular weight than glycolic acid or lactic acid. As a result, polyhydroxy acids are less penetrating than these two alpha hydroxy acids, and, as a result, provide gentler skin effects, typically with reduced irritation. Examples of suitable polyhydroxy acids include lactobionic acid, galactose, and gluconic acid.

[0054] Other personal care acids and pharmaceutical acids are known and are contemplated for use in the thickened compositions of the invention. Non-hydroxy acids that may be used are: aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N'*-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, etidronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

[0055] In order to achieve desired product performance, mixtures of different acids also may be thickened, as well as combinations of acids and the corresponding salts. Suitable such salts include the alkali metal salts of phosphoric and sulphuric acids, *e.g.* potassium biphosphate and sodium bisulphate.

[0056] The thickened topical compositions of the invention may be used where ever acidic personal care and acidic pharmaceutical preparations find utility. Accordingly, the amount of lightly- to moderately-crosslinked PVP in the composition depends on a variety of parameters, including the amount and type of acid(s), other ingredients, and the desired product form, delivery, and consumer "thickness" acceptance. For example, the thickened compositions may be an anti-aging cream, a lotion for skin blemishes, a smoothing lotion, a moisturizing composition, a skin lightening treatment, a shampoo, or a cream for use around the eyes or mouth. In these formulations the amount of lightly- to moderately-crosslinked PVP may vary from about 0.1% to about 10% (w/w) of the total formulation. More typically, however, the amount of lightly- to moderately-crosslinked PVP varies from about 1% to about 6% (w/w) of the total formulation. As illustrated in Examples 2–6, thickened acid systems containing from 43% to 71% glycolic acid were effectively thickened to viscosities ranging from 15,000 cP to 37,000 cP with the addition of 4.5% lightly- to moderately-crosslinked PVP.

[0057] At these addition levels of lightly- to moderately-crosslinked PVP, the thickened low pH

compositions typically have a Brookfield viscosity, as measured at 10 rpm and 25°C using an appropriate spindle (*e.g.*, T-C or T-E), from about 1,000 cP to about 100,000 cP. (Of course, the product Brookfield viscosity depends on the panoply of factors outlined in the preceding paragraph.) More preferably, based on the contemplated product forms, the compositions have a Brookfield viscosity from about 10,000 cP to 50,000 cP.

[0058] Because of the stabilized viscosity and pH provided by lightly- to moderately-crosslinked PVP in these low pH formulations, compositions comprising this thickener may be a sub-formulation or a complete formulation. Considering the challenges facing production scheduling, batch preparation, and formulation changes, for example, it may be advantageous to prepare a sub-formulation batch having the lightly- to moderately-crosslinked PVP, and then use portions of it at some later time to prepare one or more final formulations. Alternatively, a complete formulation with the lightly- to moderately-crosslinked PVP may be made at essentially in one batch. The compositions of Examples 2–6 may be viewed as examples of sub-formulations if they are not desired as stand-along gel preparations (*e.g.*, for skin care).

[0059] It was mentioned earlier that the amount of lightly- to moderately-crosslinked PVP in the thickened, acidic formulation depends on a number of factors, including the desired product form. The compositions do not produce "pilling" (incompatibilities and/or phase separations/agglomeration resulting in lumps) nor impart a stringy texture to the composition even at extremely low pH. This relationship between lightly- to moderately-crosslinked PVP and viscosity cannot be overstated, as thickeners generally are not known for such low pH systems.

[0060] The thickening additive compositions in accordance with this disclosure can be easily prepared by conventional methods known to persons of ordinary skill in the art, employing methods such as, simple mixing, blending, and homogenization using physical means or heat blending.

Second embodiment of the invention

[0061] In a second embodiment of the invention, the thickened topical compositions are used to deliver the personal care and/or pharmaceutical acid(s) to the skin, hair, scalp, foot, or lip of a mammal in need of treatment. As discussed for the first embodiment of the invention, it is preferred

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for this second embodiment that at least one personal care acid or at least one pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-N′-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

[0062] Again, especially preferred uses include those compositions having hydroxy acids, such as alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

[0063] As an extension of this use, it has been discovered that the use of these thickened topical compositions reduce the discomfort of irritation and sting compared to an equivalent formulation without lightly- to moderately-crosslinked PVP. The merit of this claim was provided from three independent, third-party clinical laboratory evaluations, as discussed in Examples 10–12. Without being bound to theory, one school of thought is that lightly- to moderately-crosslinked PVP in these formulas creates a gel network with the acid(s), moderates its release, and thus makes these compositions gentler on skin.

[0064] Because irritation/sting was evaluated using the simple formulas of Examples 10–12, it will be appreciated by one skilled in the art that significant formulation development may be pursued to maximize the composition and use benefits embraced by this invention. For example, products may be formulated with exfoliation, firming, moisturizing, and/or dermal perfusion effect(s) comparable to existing products (without lightly- to moderately-crosslinked PVP), but which reduce or eliminate irritation and/or sting. Such products may be found to be exceedingly gentle even on the most sensitive of skin.

[0065] Alternatively, products can be formulated that maintain the level of irritation and/or sting of current products (without lightly- to moderately-crosslinked PVP), but which provide greater exfoliation, firming, moisturizing, and/or dermal perfusion effect(s). These products may be aimed at enhanced-performance product lines, or compositions intended to be used under the care of a physician.

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Optional: Additional formulation ingredients and adjuvants

[0066] Due to the requirements of end performance, it is expected that the topical compositions of this invention will be used together with other additives to further enhance the properties of the finished product. Such ingredients may be incorporated without altering the scope of the current invention, and may be included in order to produce the necessary products.

[0067] These topical formulations inevitably have a liquid or liquid-like carrier that aides to distribute, disperse, and/or dissolve the formulation ingredients, including the lightly- to moderately-crosslinked PVP. Selection of these carriers is not limited, inasmuch as the formulations have at least one personal care acid or at least one pharmaceutical acid, and examples of liquid carriers include water, alcohols, oils, esters, and blends thereof.

[0068] The composition of the invention also can contain one or more additional additives chosen from conditioning agents, protecting agents, such as, for example, hydrosoluble, antiradical agents, antioxidants, vitamins, ultraviolet absorbers, and pro-vitamins, fixing agents, oxidizing agents, reducing agents, dyes, cleansing agents, anionic, cationic, nonionic and amphoteric surfactants, thickeners, perfumes, pearlizing agents, stabilizers, pH adjusters, filters, preservatives, cationic and nonionic polyether associative polyurethanes, polymers other than the cationic polymer described herein, vegetable oils, mineral oils, synthetic oils, polyols such as glycols and glycerol, silicones, aliphatic alcohols, colorants, bleaching agents, highlighting agents and sequestrants. These additives are present in the composition according to the invention in proportions that may range from 0% to 20% by weight in relation to the total weight of the composition. The precise amount of each additive may be easily determined by an expert in the field according to its nature and its function.

[0069] When the final product aims to protect the user from ultraviolet radiation, it may be desirable to include one or more UV absorbers. In this context, the terms *ultraviolet* and *UV* mean electromagnetic radiation, especially solar electromagnetic radiation, with a wavelength from about 100 nm to about 400 nm, and includes the UV-A, UV-B, and UV-C subclassifications of such radiation. The term *UV-A* means ultraviolet electromagnetic radiation with a wavelength from

about 320 nm to about 400 nm, and includes UV-A1 (from about 340 nm to about 400 nm) and UV-A2 (from about 320 nm to about 340 nm).

The term *UV-B* means ultraviolet electromagnetic radiation with a wavelength from about 290 nm to about 320 nm. The term *UV-C* means ultraviolet electromagnetic radiation with a wavelength from about 200 nm to about 290 nm. Finally, the term *UV absorber* means any entity that absorbs, scatters, and/or reflects any wavelength of UV radiation.

[0070] Suitable UV absorbers that may be included in the topical compositions and uses of the invention most likely will depend on local regulations. Because the rules governing the names and usage levels evolve over time, it is impossible to include every UV absorber that may be used with the invention. Typical UV absorbers include, without limitation: octyl salicylate; pentyl dimethyl PABA; octyl dimethyl PABA; benzophenone-1; benzophenone-6; 2-(2H-benzotriazole-2-yl)-4,6-di-*tert*-pentylphenol; ethyl-2-cyano-3,3-diphenylacrylate; homomenthyl salicylate; bis-ethylhexyloxyphenol methoxyphenyl triazine; methyl-(1,2,2,6,6-pentamethyl-4-piperidyl)-sebacate; 2-(2H-benzotriazole-2-yl)-4-methylphenol; diethylhexyl butamido triazone; amyl dimethyl PABA; 4,6-bis(octylthiomethyl)-*o*-cresol; CAS number 65447-77-0; red petroleum; ethylhexyl triazone; octocrylene; isoamyl-*p*-methoxycinnamate; drometrizole; titanium dioxide; 2,4-di-*tert*-butyl-6-(5-chloro-2H-benzotriazole-2-yl)-phenol; 2-hydroxy-4-octyloxybenzophenone; benzophenone-2; diisopropyl methylcinnamate; PEG-25 PABA; 2-(1,1-dimethylethyl)-6-[[3-(1,1-demethylethyl)-2-hydroxy-5-methylphenyl]methyl-4-methylphenyl acrylate; drometrizole trisiloxane; menthyl anthranilate; butyl methoxydibenzoylmethane; 2-ethoxyethyl *p*-methoxycinnamate; benzylidene camphor sulfonic acid; dimethoxyphenyl-[1-(3,4)]-4,4-dimethyl 1,3-pentanedione; zinc oxide; *N,N'*-hexane-1,6-diylbis[3-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionamide)]; pentaerythritol tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]; 2,6-di-*tert*-butyl-4-[4,6-bis(octylthio)-1,3,5-triazin-2-ylamino] phenol; 2-(2H-benzotriazole-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol; trolamine salicylate; diethylanolamine *p*-methoxycinnamate; polysilicone-15; CAS number 152261-33-1; 4-methylbenzylidene camphor; bisoctrizole; *N*-phenyl-benzenamine; reaction products with 2,4,4-trimethylpentene; sulisobenzone; (2-ethylhexyl)-2-cyano-3,3-diphenylacrylate; digalloyl trioleate; polyacrylamido methylbenzylidene camphor; glyceryl ethylhexanoate dimethoxycinnamate; 1,3-bis-[(2'-cyano-3',3'-diphenylacryloyl)oxy]-2,2-bis-{[(2'-cyano-bis-(2,2,6,6-tetramethyl-4-piperidyl)-sebacate; benzophenone-5; 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; hexamethylendiamine; benzophenone-8; ethyl-4-bis(hydroxypropyl)

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aminobenzoate; 6-*tert*-butyl-2-(5-chloro-2H-benzotriazole-2-yl)-4-methylphenol; *p*-aminobenzoic acid; 3,3′,3″,5,5′,5″-hexa-*tert*-butyl-α-α′-α″-(mesitylene-2,4,6-triyl)tri-*p*-cresol; lawsone with dihydroxyacetone; benzophenone-9; benzophenone-4; ethylhexyl dimethoxy benzylidene dioxoimidazoline propionate; *N,N′*-bisformyl-N,N′-bis-(2,2,6,6-tetramethyl-4-piperidinyl)-; 3-benzylidene camphor; terephthalylidene dicamphor sulfonic acid; camphor benzalkonium methosulfate; bisdisulizole disodium; etocrylene; ferulic acid; 2-(2H-benzotriazole-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phenol; 4,6-bis(dodecylthiomethyl)-*o*-cresol; β-2-glucopyranoxy propyl hydroxy benzophenone; phenylbenzimidazole sulfonic acid; benzophenone-3; diethylamine hydroxybenzoyl hexylbenzoate; 3′,3′-diphenylacryloyl)oxy]methyl}-propane; ethylhexyl *p*-methoxycinnamate, and blends thereof.

[0071] For example, the compositions according to the invention may be used to moisturize, soothe, retain moisture, and/or smooth skin, especially skin of the hands, elbows, and feet, and around the eyes and mouth. Highly preferred are thickened formulations that are non-greasy, such as lotions having glycerin, caprylic/capric triglycerides, hydrogenated cocoglycerides, and/or one or more vegetable oils (*e.g.*, helianthus oil, soybean oil, linseed oil, and olive oil).

[0072] Any known conditioning agent is useful in the personal care compositions of this invention. Conditioning agents function to improve the cosmetic properties of the hair, particularly softness, thickening, untangling, feel, and static electricity and may be in liquid, semi-solid, or solid form such as oils, waxes, or gums. Similarly, any known skin altering agent is useful in the compositions of this invention. Preferred conditioning agents include cationic polymers, cationic surfactants and cationic silicones.

[0073] Conditioning agents may be chosen from synthesis oils, mineral oils, vegetable oils, fluorinated or perfluorinated oils, natural or synthetic waxes, silicones, cationic polymers, proteins and hydrolyzed proteins, ceramide type compounds, cationic surfactants, fatty amines, fatty acids and their derivatives, as well as mixtures of these different compounds.

[0074] The synthesis oils include polyolefins, *e.g.*, poly-α-olefins such as polybutenes, polyisobutenes and polydecenes. The polyolefins can be hydrogenated.

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[0075] The mineral oils suitable for use in the compositions of the invention include hexadecane and oil of paraffin.

[0076] A list of suitable animal and vegetable oils comprises sunflower, corn, soy, avocado, jojoba, squash, raisin seed, sesame seed, walnut oils, fish oils, glycerol tricaprocaprylate, Purcellin oil or liquid jojoba, and blends thereof.

[0077] Suitable natural or synthetic oils include eucalyptus, lavender, vetiver, litsea cubeba, lemon, sandalwood, rosemary, chamomile, savory, nutmeg, cinnamon, hyssop, caraway, orange, geranium, cade, and bergamot.

[0078] Suitable natural and synthetic waxes include carnauba wax, candelila wax, alfa wax, paraffin wax, ozokerite wax, vegetable waxes such as olive wax, rice wax, hydrogenated jojoba wax, absolute flower waxes such as black currant flower wax, animal waxes such as bees wax, modified bees wax (cerabellina), marine waxes and polyolefin waxes such as polyethylene wax, and blends thereof.

[0079] The cationic polymers that may be used as a conditioning agent according to the invention are those known to improve the cosmetic properties of hair treated by detergent compositions. The expression "cationic polymer" as used herein, indicates any polymer containing cationic groups and/or ionizable groups in cationic groups. The cationic polymers used generally have a molecular weight the average number of which falls between about 500 Da and 5,000,000 Da and preferably between 1000 Da and 3,000,000 Da.

[0080] The preferred cationic polymers are chosen from among those containing units including primary, secondary, tertiary, and/or quaternary amine groups that may either form part of the main polymer chain or a side chain.

[0081] Useful cationic polymers include known polyamine, polyaminoamide, and quaternary polyammonium types of polymers, such as:

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[0082] (1) homopolymers and copolymers derived from acrylic or methacrylic esters or amides. The copolymers can contain one or more units derived from acrylamides, methacrylamides, diacetone acrylamides, acrylamides and methacrylamides, acrylic or methacrylic acids or their esters, vinyllactams such as vinyl pyrrolidone or vinyl caprolactam, and vinyl esters. Specific examples include: copolymers of acrylamide and dimethyl amino ethyl methacrylate quaternized with dimethyl sulfate or with an alkyl halide; copolymers of acrylamide and methacryloyl oxyethyl trimethyl ammonium chloride; the copolymer of acrylamide and methacryloyl oxyethyl trimethyl ammonium methosulfate; copolymers of vinyl pyrrolidone/dialkylaminoalkyl acrylate or methacrylate, optionally quaternized, such as the products sold under the name Gafquat® by International Specialty Products; the dimethyl amino ethyl methacrylate/vinyl caprolactam/vinyl pyrrolidone terpolymers, such as the product sold under the name Gaffix® VC 713 by International Specialty Products; the vinyl pyrrolidone/methacrylamidopropyl dimethylamine copolymer, marketed under the name Styleze® CC 10 by International Specialty Products; and the vinyl pyrrolidone/quaternized dimethyl amino propyl methacrylamide copolymers such as the product sold under the name Gafquat® HS 100 by International Specialty Products (Wayne, NJ).

[0083] (2) derivatives of cellulose ethers containing quaternary ammonium groups, such as hydroxy ethyl cellulose quaternary ammonium that has reacted with an epoxide substituted by a trimethyl ammonium group.

[0084] (3) derivatives of cationic cellulose such as cellulose copolymers or derivatives of cellulose grafted with a hydrosoluble quaternary ammonium monomer, as described in U.S. patent 4,131,576, such as the hydroxy alkyl cellulose, and the hydroxymethyl-, hydroxyethyl- or hydroxypropyl- cellulose grafted with a salt of methacryloyl ethyl trimethyl ammonium, methacrylamidopropyl trimethyl ammonium, or dimethyl diallyl ammonium.

[0085] (4) cationic polysaccharides such as described in U.S. patents 3,589,578 and 4,031,307, guar gums containing cationic trialkyl ammonium groups and guar gums modified by a salt, *e.g.*, chloride of 2,3-epoxy propyl trimethyl ammonium.

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[0086] (5) polymers composed of piperazinyl units and alkylene or hydroxy alkylene divalent radicals with straight or branched chains, possibly interrupted by atoms of oxygen, sulfur, nitrogen, or by aromatic or heterocyclic cycles, as well as the products of the oxidation and/or quaternization of such polymers.

[0087] (6) water-soluble polyamino amides prepared by polycondensation of an acid compound with a polyamine. These polyamino amides may be reticulated.

[0088] (7) derivatives of polyamino amides resulting from the condensation of polyalcoylene polyamines with polycarboxylic acids followed by alcoylation by bi-functional agents.

[0089] (8) polymers obtained by reaction of a polyalkylene polyamine containing two primary amine groups and at least one secondary amine group with a dioxycarboxylic acid chosen from among diglycolic acid and saturated dicarboxylic aliphatic acids having 3 to 8 atoms of carbon. Such polymers are described in U.S. Patents 3,227,615 and 2,961,347.

[0090] (9) the cyclopolymers of alkyl dialyl amine or dialkyl diallyl ammonium such as the homopolymer of dimethyl diallyl ammonium chloride and copolymers of diallyl dimethyl ammonium chloride and acrylamide.

[0091] (10) quaternary diammonium polymers such as hexadimethrine chloride.

[0092] (11) quaternary polyammonium polymers, including, for example, Mirapol® A 15, Mirapol® AD1, Mirapol® AZ1, and Mirapol® 175 products sold by Miranol .

[0093] (12) the quaternary polymers of vinyl pyrrolidone and vinyl imidazole such as the products sold under the names Luviquat® FC 905, FC 550, and FC 370 by BASF Corporation.

[0094] (13) quaternary polyamines.

[0095] (14) reticulated polymers known in the art.

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[0096] Other cationic polymers that may be used within the context of the invention are cationic proteins or hydrolyzed cationic proteins, polyalkyleneimines such as polyethyleneimines, polymers containing vinyl pyridine or vinyl pyridinium units, condensates of polyamines and epichlorhydrins, quaternary polyurethanes, and derivatives of chitin.

[0097] Preferred cationic polymers are derivatives of quaternary cellulose ethers, the homopolymers and copolymers of dimethyl diallyl ammonium chloride, quaternary polymers of vinyl pyrrolidone and vinyl imidazole, and mixtures thereof.

[0098] The conditioning agent can be any silicone known by those skilled in the art to be useful as a conditioning agent. The silicones suitable for use according to the invention include polyorganosiloxanes that are insoluble in the composition. The silicones may be present in the form of oils, waxes, resins, or gums. They may be volatile or non-volatile. The silicones can be selected from polyalkyl siloxanes, polyaryl siloxanes, polyalkyl aryl siloxanes, silicone gums and resins, and polyorgano siloxanes modified by organofunctional groups, and mixtures thereof.

[0099] Suitable polyalkyl siloxanes include polydimethyl siloxanes with terminal trimethyl silyl groups or terminal dimethyl silanol groups (dimethiconol) and polyalkyl (C_1-C_{20}) siloxanes.

[00100] Suitable polyalkyl aryl siloxanes include polydimethyl methyl phenyl siloxanes and polydimethyl diphenyl siloxanes, linear or branched.

[00101] The silicone gums suitable for use herein include polydiorganosiloxanes preferably having a number-average molecular weight between 200,000 Da and 1,000,000, Da used alone or mixed with a solvent. Examples include polymethyl siloxane, polydimethyl siloxane/methyl vinyl siloxane gums, polydimethyl siloxane/diphenyl siloxane, polydimethyl siloxane/phenyl methyl siloxane and polydimethyl siloxane/diphenyl siloxane/methyl vinyl siloxane.

[00102] Suitable silicone resins include silicones with a dimethyl/trimethyl siloxane structure and resins of the trimethyl siloxysilicate type.

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[00103] The organo-modified silicones suitable for use in the invention include silicones such as those previously defined and containing one or more organofunctional groups attached by means of a hydrocarbon radical and grafted siliconated polymers. Particularly preferred are amino functional silicones.

[00104] The silicones may be used in the form of emulsions, nano-emulsions, or micro-emulsions.

[00105] The conditioning agent can be a protein or hydrolyzed cationic or non-cationic protein. Examples of these compounds include hydrolyzed collagens having triethyl ammonium groups, hydrolyzed collagens having trimethyl ammonium and trimethyl stearyl ammonium chloride groups, hydrolyzed animal proteins having trimethyl benzyl ammonium groups (benzyltrimonium hydrolyzed animal protein), hydrolyzed proteins having groups of quaternary ammonium on the polypeptide chain, including at least one C_1-C_{18} alkyl.

[00106] Hydrolyzed proteins include Croquat L, in which the quaternary ammonium groups include a C_{12} alkyl group, Croquat M, in which the quaternary ammonium groups include C_{10}-C_{18} alkyl groups, Croquat S in which the quaternary ammonium groups include a C_{18} alkyl group and Crotein Q in which the quaternary ammonium groups include at least one C_1-C_{18} alkyl group. These products are sold by Croda.

[00107] The conditioning agent can comprise quaternized vegetable proteins such as wheat, corn, or soy proteins such as cocodimonium hydrolyzed wheat protein, laurdimonium hydrolyzed wheat protein and steardimonium hydrolyzed wheat protein, 2-N-stearoyl amino-octadecane-1,3-diol, 2-*N*-behenoyl amino-octadecane-1,3-diol, 2-*N*-[2-hydroxy-palmitoyl]-amino-octadecane-1,3-diol, 2-*N*-stearoyl amino-octadecane-1,3,4-triol, *N*-stearoyl phytosphingosine, 2-*N*-palmitoyl amino-hexadecane-1,3-diol, bis-(*N*-hydroxy ethyl N-cetyl) malonamide, *N*-(2-hydroxy ethyl)-*N*-(3-cetoxyl-2-hydroxy propyl) amide of cetylic acid, *N*-docosanoyl *N*-methyl-D-glucamine and mixtures of such compounds.

[00108] The conditioning agent can be a cationic surfactant such as a salt of a primary, secondary, or tertiary fatty amine, optionally polyoxyalkylenated, a quaternary ammonium salt, a derivative of

imadazoline, or an amine oxide. Suitable examples include mono-, di-, or tri- alkyl quaternary ammonium compounds with a counterion such as a chloride, methosulfate, tosylate, etc. including, but not limited to, cetrimonium chloride, dicetyldimonium chloride, behentrimonium methosulfate, and the like. The presence of a quaternary ammonium compound in conjunction with the polymer described above reduces static and enhances combing of hair in the dry state. The polymer also enhances the deposition of the quaternary ammonium compound onto the hair substrate thus enhancing the conditioning effect of hair.

[00109] The conditioning agent can be any fatty amine known to be useful as a conditioning agent; *e.g.* dodecyl, cetyl or stearyl amines, such as stearamidopropyl dimethylamine.

[00110] The conditioning agent can be a fatty acid or derivatives thereof known to be useful as conditioning agents. Suitable fatty acids include myristic acid, palmitic acid, stearic acid, behenic acid, oleic acid, linoleic acid, and isostearic acid. The derivatives of fatty acids include carboxylic ester acids including mono-, di-, tri- and tetra- carboxylic acids.

[00111] The conditioning agent can be a fluorinated or perfluorinated oil. The fluoridated oils may also be fluorocarbons such as fluoramines, *e.g.*, perfluorotributylamine, fluoridated hydrocarbons, such as perfluorodecahydronaphthalene, fluoroesters, and fluoroethers.

[00112] Of course, mixtures of two or more conditioning agents can be used.

[00113] The conditioning agent or agents can be present in an amount of 0.001% to 20%, preferably from 0.01% to 10%, and even more preferably from 0.1% to 3% by weight based on the total weight of the final composition.

[00114] The antioxidants or antiradical agents can be selected from phenols such as BHA (*tert*-butyl-4-hydroxy anisole), BHT (2,6-di-*tert*-butyl-p-cresol), TBHQ (*tert*-butyl hydroquinone), polyphenols such as proanthocyanodic oligomers, flavonoids, hindered amines such as tetra amino piperidine, erythorbic acid, polyamines such as spermine, cysteine, glutathione, superoxide dismutase, and lactoferrin.

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[00115] The vitamins can be selected from ascorbic acid (vitamin C), vitamin E, vitamin E acetate, vitamin E phosphate, B vitamins such as B3 and B5, niacin, vitamin A, and derivatives thereof. The provitamins can be selected from panthenol and retinol.

[00116] The protecting agent can be present in an amount 0.001% to 20% by weight, preferably from 0.01% to 10% by weight, and more preferably 0.1 to 5% by weight of the total weight of the final composition.

[00117] In addition, the compositions according to the invention advantageously include at least one surfactant, which can be present in an amount of 0.1% and 60% preferably 1% and 40%, and more preferably 5% and 30% by weight based on the total weight of the composition. The surfactant may be chosen from among anionic, amphoteric, or non-ionic surfactants, or mixtures of them known to be useful in personal care compositions.

[00118] Additional thickeners or viscosity increasing agents may be included in the composition of the invention, such as: Acetamide MEA; acrylamide/ethalkonium chloride acrylate copolymer; acrylamide/ethyltrimonium chloride acrylate/ethalkonium chloride acrylate copolymer; acrylamides copolymer; acrylamide/sodium acrylate copolymer; acrylamide/sodium acryloyldimethyltaurate copolymer; acrylates/acetoacetoxyethyl methacrylate copolymer; acrylates/beheneth-25 methacrylate copolymer; acrylates/C_{10}-C_{30} alkyl acrylate crosspolymer; acrylates/ceteth-20 itaconate copolymer; acrylates/ceteth-20 methacrylate copolymer; acrylates/laureth-25 methacrylate copolymer; acrylates/palmeth-25 acrylate copolymer; acrylates/palmeth-25 itaconate copolymer; acrylates/steareth-50 acrylate copolymer; acrylates/steareth-20 itaconate copolymer; acrylates/steareth-20 methacrylate copolymer; acrylates/stearyl methacrylate copolymer; acrylates/vinyl isodecanoate crosspolymer; acrylic acid/acrylonitrogens copolymer; adipic acid/methyl DEA crosspolymer; agar; agarose; alcaligenes polysaccharides; algin; alginic acid; almondamide DEA; almondamidopropyl betaine; aluminum/magnesium hydroxide stearate; ammonium acrylates/acrylonitrogens copolymer; ammonium acrylates copolymer; ammonium acryloyldimethyltaurate/vinyl formamide copolymer; ammonium acryloyldimethyltaurate/VP copolymer; ammonium alginate; ammonium chloride; ammonium polyacryloyldimethyl taurate; ammonium sulfate; amylopectin; apricotamide DEA; apricotamidopropyl betaine; arachidyl

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alcohol; arachidyl glycol; arachis hypogaea (peanut) flour; ascorbyl methylsilanol pectinate; astragalus gummifer gum; attapulgite; avena sativa (oat) kernel flour; avocadamide DEA; avocadamidopropyl betaine; azelamide MEA; babassuamide DEA; babassuamide MEA; babassuamidopropyl betaine; behenamide DEA; behenamide MEA; behenamidopropyl betaine; behenyl betaine; bentonite; butoxy chitosan; caesalpinia spinosa gum; calcium alginate; calcium carboxymethyl cellulose; calcium carrageenan; calcium chloride; calcium potassium carbomer; calcium starch octenylsuccinate; C20-40 alkyl stearate; canolamidopropyl betaine; capramide DEA; capryl/capramidopropyl betaine; carbomer; carboxybutyl chitosan; carboxymethyl cellulose acetate butyrate; carboxymethyl chitin; carboxymethyl chitosan; carboxymethyl dextran; carboxymethyl hydroxyethylcellulose; carboxymethyl hydroxypropyl guar; carnitine; cellulose acetate propionate carboxylate; cellulose gum; ceratonia siliqua gum; cetearyl alcohol; cetyl alcohol; cetyl babassuate; cetyl betaine; cetyl glycol; cetyl hydroxyethylcellulose; chimyl alcohol; cholesterol/HDI/pullulan copolymer; cholesteryl hexyl dicarbamate pullulan; citrus aurantium dulcis (orange) peel extract; cocamide DEA; cocamide MEA; cocamide MIPA; cocamidoethyl betaine; cocamidopropyl betaine; cocamidopropyl hydroxysultaine; coco-betaine; coco-hydroxysultaine; coconut alcohol; coco/oleamidopropyl betaine; coco-Sultaine; cocoyl sarcosinamide DEA; cornamide/cocamide DEA; cornamide DEA; croscarmellose; crosslinked bacillus/glucose/sodium glutamate ferment; cyamopsis tetragonoloba (guar) gum; decyl alcohol; decyl betaine; dehydroxanthan gum; dextrin; dibenzylidene sorbitol; diethanolaminooleamide DEA; diglycol/CHDM/isophthalates/SIP copolymer; dihydroabietyl behenate; dihydrogenated tallow benzylmonium hectorite; dihydroxyaluminum aminoacetate; dimethicone/PEG-10 crosspolymer; dimethicone/PEG-15 crosspolymer; dimethicone propyl PG-betaine; dimethylacrylamide/acrylic acid/polystyrene ethyl methacrylate copolymer; dimethylacrylamide/sodium acryloyldimethyltaurate crosspolymer; disteareth-100 IPDI; DMAPA acrylates/acrylic acid/acrylonitrogens copolymer; erucamidopropyl hydroxysultaine; ethylene/sodium acrylate copolymer; gelatin; gellan gum; glyceryl alginate; glycine soja (soybean) flour; guar hydroxypropyltrimonium chloride; hectorite; hyaluronic acid; hydrated silica; hydrogenated potato starch; hydrogenated tallow; hydrogenated tallowamide DEA; hydrogenated tallow betaine; hydroxybutyl methylcellulose; hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer; hydroxyethylcellulose; hydroxyethyl chitosan; hydroxyethyl ethylcellulose; hydroxyethyl stearamide-MIPA; hydroxylauryl/hydroxymyristyl betaine; hydroxypropylcellulose; hydroxypropyl chitosan; hydroxypropyl ethylenediamine carbomer; hydroxypropyl guar; hydroxypropyl methylcellulose; hydroxypropyl methylcellulose stearoxy

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ether; hydroxypropyl starch; hydroxypropyl starch phosphate; hydroxypropyl xanthan gum; hydroxystearamide MEA; isobutylene/sodium maleate copolymer; isostearamide DEA; isostearamide MEA; isostearamide mIPA; isostearamidopropyl betaine; lactamide MEA; lanolinamide DEA; lauramide DEA; lauramide MEA; lauramide MIPA; lauramide/myristamide DEA; lauramidopropyl betaine; lauramidopropyl hydroxysultaine; laurimino bispropanediol; lauryl alcohol; lauryl betaine; lauryl hydroxysultaine; lauryl/myristyl glycol hydroxypropyl ether; lauryl sultaine; lecithinamide DEA; linoleamide DEA; linoleamide MEA; linoleamide MIPA; lithium magnesium silicate; lithium magnesium sodium silicate; macrocystis pyrifera (kelp); magnesium alginate; magnesium/aluminum/hydroxide/carbonate; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate; methoxy PEG-22/dodecyl glycol copolymer; methylcellulose; methyl ethylcellulose; methyl hydroxyethylcellulose; microcrystalline cellulose; milkamidopropyl betaine; minkamide DEA; minkamidopropyl betaine; MIPA-myristate; montmorillonite; Moroccan lava clay; myristamide DEA; myristamide MEA; myristamide MIPA; myristamidopropyl betaine; myristamidopropyl hydroxysultaine; myristyl alcohol; myristyl betaine; natto gum; nonoxynyl hydroxyethylcellulose; oatamide MEA; oatamidopropyl betaine; octacosanyl glycol isostearate; octadecene/MA copolymer; oleamide DEA; oleamide MEA; oleamide MIPA; oleamidopropyl betaine; oleamidopropyl hydroxysultaine; oleyl betaine; olivamide DEA; olivamidopropyl betaine; oliveamide MEA; palmamide DEA; palmamide MEA; palmamide MIPA; palmamidopropyl betaine; palmitamide DEA; palmitamide MEA; palmitamidopropyl betaine; palm kernel alcohol; palm kernelamide DEA; palm kernelamide MEA; palm kernelamide MIPA; palm kernelamidopropyl betaine; peanutamide MEA; peanutamide MIPA; pectin; PEG-800; PEG-crosspolymer; PEG-150/decyl alcohol/SMDI copolymer; PEG-175 diisostearate; PEG-190 distearate; PEG-15 glyceryl tristearate; PEG-140 glyceryl tristearate; PEG-240/HDI copolymer bis-decyltetradeceth-20 ether; PEG-100/IPDI copolymer; PEG-180/laureth-50/TMMG copolymer; PEG-10/lauryl dimethicone crosspolymer; PEG-15/lauryl dimethicone crosspolymer; PEG-2M; PEG-5M; PEG-7M; PEG-9M; PEG-14M; PEG-20M; PEG-23M; PEG-25M; PEG-45M; PEG-65M; PEG-90M; PEG-115M; PEG-160M; PEG-180M; PEG-120 methyl glucose trioleate; PEG-180/octoxynol-40/TMMG copolymer; PEG-150 pentaerythrityl tetrastearate; PEG-4 rapeseedamide; PEG-150/stearyl alcohol/SMDI copolymer; phaseolus angularis seed powder; polianthes tuberosa extract; polyacrylate-3; polyacrylic acid; polycyclopentadiene; polyether-1; polyethylene/isopropyl maleate/MA copolyol; polyglyceryl-3 disiloxane dimethicone; polyglyceryl-3 polydimethylsiloxyethyl dimethicone; polymethacrylic acid; polyquaternium-52; polyvinyl

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alcohol; potassium alginate; potassium aluminum polyacrylate; potassium carbomer; potassium carrageenan; potassium chloride; potassium palmate; potassium polyacrylate; potassium sulfate; potato starch modified; PPG-2 cocamide; PPG-1 hydroxyethyl caprylamide; PPG-2 hydroxyethyl cocamide; PPG-2 hydroxyethyl coco/isostearamide; PPG-3 hydroxyethyl soyamide; PPG-14 laureth-60 hexyl dicarbamate; PPG-14 laureth-60 isophoryl dicarbamate; PPG-14 palmeth-60 hexyl dicarbamate; propylene glycol alginate; PVP/decene copolymer; PVP montmorillonite; pyrus cydonia seed; pyrus malus (apple) fiber; rhizobian gum; ricebranamide DEA; ricinoleamide DEA; ricinoleamide MEA; ricinoleamide MIPA; ricinoleamidopropyl betaine; ricinoleic acid/adipic acid/AEEA copolymer; rosa multiflora flower wax; sclerotium gum; sesamide DEA; sesamidopropyl betaine; sodium acrylate/acryloyldimethyl taurate copolymer; sodium acrylates/acrolein copolymer; sodium acrylates/acrylonitrogens copolymer; sodium acrylates copolymer; sodium acrylates crosspolymer; sodium acrylate/sodium acrylamidomethylpropane sulfonate copolymer; sodium acrylates/vinyl isodecanoate crosspolymer; sodium acrylate/vinyl alcohol copolymer; sodium carbomer; sodium carboxymethyl chitin; sodium carboxymethyl dextran; sodium carboxymethyl beta-glucan; sodium carboxymethyl starch; sodium carrageenan; sodium cellulose sulfate; sodium chloride; sodium cyclodextrin sulfate; sodium hydroxypropyl starch phosphate; sodium isooctylene/MA copolymer; sodium magnesium fluorosilicate; sodium oleate; sodium palmitate; sodium palm kernelate; sodium polyacrylate; sodium polyacrylate starch; sodium polyacryloyldimethyl taurate; sodium polygamma-glutamate; sodium polymethacrylate; sodium polystyrene sulfonate; sodium silicoaluminate; sodium starch octenylsuccinate; sodium stearate; sodium stearoxy PG-hydroxyethylcellulose sulfonate; sodium styrene/acrylates copolymer; sodium sulfate; sodium tallowate; sodium tauride acrylates/acrylic acid/acrylonitrogens copolymer; sodium tocopheryl phosphate; solanum tuberosum (potato) starch; soyamide DEA; soyamidopropyl betaine; starch/acrylates/acrylamide copolymer; starch hydroxypropyltrimonium chloride; stearamide AMP; stearamide DEA; stearamide DEA-distearate; stearamide DIBA-stearate; stearamide MEA; stearamide MEA-stearate; stearamide MIPA; stearamidopropyl betaine; steareth-60 cetyl ether; steareth-100/PEG-136/HDI copolymer; stearyl alcohol; stearyl betaine; sterculia urens gum; synthetic fluorphlogopite; tallamide DEA; tallow alcohol; tallowamide DEA; tallowamide MEA; tallowamidopropyl betaine; tallowamidopropyl hydroxysultaine; tallowamine oxide; tallow betaine; tallow dihydroxyethyl betaine; tamarindus indica seed gum; tapioca starch; TEA-alginate; TEA-carbomer; TEA-hydrochloride; trideceth-2 carboxamide MEA; tridecyl alcohol; triethylene glycol dibenzoate; trimethyl pentanol hydroxyethyl ether; triticum vulgare

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(wheat) germ powder; triticum vulgare (wheat) kernel flour; triticum vulgare (wheat) starch; tromethamine acrylates/acrylonitrogens copolymer; tromethamine magnesium aluminum silicate; undecyl alcohol; undecylenamide DEA; undecylenamide MEA; undecylenamidopropyl betaine; welan gum; wheat germamide DEA; wheat germamidopropyl betaine; xanthan gum; yeast beta-glucan; yeast polysaccharides and zea mays (corn) starch.

Product forms

[00119] Acknowledging the many ways topical personal care and pharmaceutical compositions may be used, it is within the scope of the invention that the thickened compositions may have the form of a solution, a cream, an ointment, a lotion, an oil-in-water emulsion, a water-in-oil emulsion, a shampoo, a spray, a gel, a wash, a rinse, an aerosol, a suspension, a paste, a powder, a serum, or a mousse.

[00120] In other examples of the invention, thickened compositions may be used to wash and treat keratinous material such as hair, skin, eyelashes, eyebrows, fingernails, lips, and hairy skin. The compositions of the invention may also take the form of skin-washing compositions, and particularly in the form of solutions or gels for the bath or shower, or of make-up removal products.

[00121] The compositions according to the invention may also take the form of after-shampoo compositions, to be rinsed off or not, for permanents, straightening, waving, dyeing, or bleaching, or the form of rinse compositions to be applied before or after dyeing, bleaching, permanents, straightening, relaxing, waving or even between the two stages of a permanent or straightening process.

[00122] Examples of related compositions are disclosed in U.S. patents 5,599,800; 5,650,166; 5,916,549; and 6,812,192; U.S. patent application 2009/0317432; EP 556,660; 661,037; 661,038; 662,315; 676,194; 796,077; 970,682; 976383; 1,415,654; and 2,067,467; and WO 2005/032506; each of which is incorporated herein its entirety by reference.

[00123] The compositions according to the invention can be detergent compositions such as shampoos, bath gels, and bubble baths. In this mode, the compositions will comprise water as a

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liquid carrier. The surfactant or surfactants that form the washing base may be chosen alone or in blends, from known anionic, amphoteric, or non-ionic surfactants. The quantity and quality of the washing base must be sufficient to impart a satisfactory foaming and/or detergent value to the final composition. The washing base can be from 4% to 50% by weight, preferably from 6% to 35% by weight, and even more preferentially from 8% to 25% by weight of the total weight of the final composition.

[00124] Cosmetic compositions according to the invention may, for example, be used as care and/or sun protection product for the face and/or the body having a consistency ranging from liquid to semiliquid (*e.g.*, milks, creams), and gels, creams, pastes, powders (including compacted powders), and wax-like compositions (*e.g.*, lip balms).

[00125] For compositions intended to protect the hair from UV radiation, suitable product forms include, but not limited to: conditioners, dispersions, emulsions, gels, lotions, mists, mousses, shampoos, and sprays.

[00126] The personal care active includes shampoo, body wash products, shaving cream, hand soap, bubble bath, bath gel, after-shave lotions, creams, moisturizers, sunscreens, liquid soaps, color cosmetics, acid peels, perms, hair color, sunless tanning and conditioners.

[00127] Due to the low pH of these topical compositions, they may be expected provide a skin exfoliation effect (also known as keratolysis). As such, these acidic formulations find use in treating wrinkles and dry skin. Other skin and scalp conditions that can be treated by these thickened, low pH compositions also are contemplated, for example, the use of thickened salicylic acid formulations for the treatment of various warts, corns, and calluses. Examples of wart-removal compositions include the following, each of which is incorporated herein its entirety by reference: U.S. patents 5,962,011 and 7,655,668; US patent application 2007/0280972; EP 1,002,530; and WO 2009/085890. Examples of skin lightening compositions and age-spot compositions include the following, each of which is incorporated herein its entirety by reference: U.S. 5,747,051; U.S. patent application 2008/0214669; EP 1028723; and WO 2004/073745.

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[00128] The following examples are presented to illustrate specific embodiments of the present compositions and methods. These examples should not be interpreted as limitations upon the scope of the invention.

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EXAMPLES

Example 1: Ascorbic acid and glycolic acid gels

[00129] Two formulations were prepared containing 10% ascorbic acid or 10% glycolic acid in water with 5% lightly- to moderately-crosslinked PVP (Table 1). Neither composition phase separated or coagulated, but rather both were smooth, low pH gels as indicated in Table 1.

[00130] Table 1: Low pH glycolic acid and ascorbic acid gels of Example 1.

active	liquid carrier	lightly- to moderately-crosslinked PVP	initial pH[†]	viscosity[*]
10% ascorbic acid	water	5%	3.88	23,000
10% glycolic acid	water	5%	3.92	13,500

[†]pH was measured at 25°C.

[*]Viscosity was measured using a Brookfield LVT viscometer with spindle T-E at 10 rpm and 25°C.

Examples 2–6: Thickened acidic systems having lightly- to moderately-crosslinked PVP

[00131] Five low pH compositions of the invention were made by blending between 4.5%–6.0% lightly- to moderately-crosslinked PVP, a personal care acid, and at least one liquid carrier (Table 2). The five preparations were smooth gels having a pH less than 3.0 and viscosities of 15,000 cP or more.

[00132] Thickened acidic systems such as these may represent stand-alone formulations. Alternatively, their pH and viscosity stability allows them to be treated as sub-formulations to be prepared in advance, and then to be added to other ingredients as necessary.

[00133] Table 2: Thickened acidic systems of Examples 2-6

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ex.	ingredients	addition level (% w/w)	appearance	pH†	viscosity*
2	lightly- to moderately-crosslinked PVP	4.5	gel	1.68	15,000
	glycolic acid, (70% solution)	43.0			
	deionized water	52.5			
	total	100.0			
3	lightly- to moderately-crosslinked PVP	6.0	gel	2.9	22,000
	salicylic acid, USP	10.0			
	SD alcohol 40	84.0			
	total	100.0			
4	lightly- to moderately-crosslinked PVP	4.5	gel	1.32	30,000
	glycolic acid, (70% solution)	71.0			
	deionized water	24.5			
	total	100.			
5	lightly- to moderately-crosslinked PVP	4.5	gel	1.35	35,000
	glycolic acid, (70% solution)	71.0			
	deionized water	14.5			
	SD alcohol 40	10.0			
	total	100.0			
6	lightly- to moderately-crosslinked PVP	4.5	gel	1.45	37,000
	glycolic acid (70% solution)	71.0			
	deionized water	4.5			
	SD alcohol 40	20.0			
	total	100.0			

†pH was measured at 25°C.

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*Viscosity measured using a Brookfield LVT viscometer with spindle T-C at 10 rpm and 25°C.

Example 7: Acne gel preparation

[00134] An acne gel preparation was made containing two active ingredients, 2% salicylic acid and 5% glycolic acid (Table 3). First, salicylic acid was dissolved in ethanol, to which water and glycolic then were added with mixing. The pH of this sub-formulation was adjusted to 4.2 using ammonium hydroxide solution. Then, lightly- to moderately crosslinked PVP was added followed by homogenization. To this thickened gel two emollients (Ceraphyl® 41 and Lubrajel® Oil) were added.

[00135] The preparation described above appeared as a gel, and the measured pH was 4. The viscosity, measured by a Brookfield RVT viscometer using spindle T-C at 10 rpm and 25°C was 24,000 cP.

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[00136] Table 3: Acne gel formulation of Example 7.

ingredient		addition level (% w/w)
Phase A		
water		38.9
salicylic acid		2.0
glycolic acid (70%)		7.2
ammonium hydroxide solution (28%–30%)		1.4
	total	49.5
Phase B		
ethanol		40.0
lightly- to moderately-crosslinked PVP		5.0
	total	45.0
Phase C		
Ceraphyl® 41		3.0
Lubrajel® Oil		2.5
	total	5.5
	grand total	**100.0**

Example 8: Stability of acne gel preparation of Example 7

[00137] The acne gel of Example 7 was placed on stability testing at 5°C, 25°C, and 45°C to determine if viscosity or pH changed over time or after freeze / thaw cycles. Viscosity was measured using a Brookfield RVT viscometer with an T-C spindle at 10 rpm. Freeze / thaw cycles were defined as freezing overnight at -15°C, followed by next morning thaw at 25°C until the acne gel reached 25°C.

[00138] Measured viscosities at 5°C and 25°C were essentially constant over the 12 week test period (Figure 1). Storage at 45°C produced slightly increased viscosity, from an initial value of 24,000 cP to 32,000 cP.

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[00139] Like viscosity, pH was essentially constant over the 12 week stability period. At 5°C storage the acne gel pH remained essentially constant, while at 25°C and 45°C a small increase of about 0.2 unit was recorded (Figure 2).

Example 9: Crème brûlée skin renewal treatment formulation

[00140] A renewal treatment for dry, slack, rough, and/or wrinkled skin was prepared containing the ingredients and amounts shown in Table 4. This formula was made by preparing Phase A with moderate mixing, followed by separate preparation of Phase B, adjusting the pH with ammonium hydroxide to a pH of 3.8–4.2. Then, Phase B was mixed in to Phase A, and the resulting blend was heated to 75°C. In a different beaker, the ingredients of Phase C were combined and heated to 75°C. Then, Phase A-B and Phase C were combined and mixed for 5 minutes. The combination then was homogenized to 65°C–70°C, followed by mixing. After this step, Phase D was prepared and added to the combination of Phases A-B-C. When the final product cooled to 40°C, mixing was stopped, and allowed to thicken overnight.

[00141] The crème brûlée skin renewal treatment formula had a final appearance of a smooth, off-white cream / gel. The viscosity, measured by a Brookfield RVT viscometer using spindle T-C at 10 rpm, was 40,000 cP – 42,000 cP.

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[00142] Table 4: Crème brûlée skin renewal formulation of Example 9

ingredient		addition level (% w/w)
Phase A		
deionized water		36.6
lightly- to moderately-crosslinked PVP		3.5
propylene Glycol		2.0
disodium EDTA		0.1
	total	42.2
Phase B		
deionized water		20.0
glycolic acid (70% active solution)		11.4
citric acid, anhydrous USP		2.0
ammonium hydroxide (28% active solution)		2.8
	total	36.2
Phase C		
dicetyl phosphate, ceteth-10 phosphate		3.5
cetearyl alcohol		2.5
isodecyl neopentanoate		2.5
isocetyl stearate		2.0
decyl oleate		2.25
shea butter		0.75
dimethicone		0.75
	total	14.25
Phase D		
disodium lauriminodipropionate tocopheryl phosphates		0.75
diazolidinyl urea and iodopropynyl butylcarbamate		0.6
Collaxyl		2.0

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Orsirtine		1.0
Achromaxyl IS		3.0
	total	7.35
	grand total	**100.0**

Example 10: Reduced sting with tartaric acid solution

[00143] An independent, third-party clinical laboratory evaluated sting as a consumer perception of irritation for two formulations. The first formula was a 0.5% tartaric acid aqueous solution, and the second formula was an example of the invention, being identical to the first except it additionally contained 5% lightly- to moderately-crosslinked PVP. The facial discomfort assay test was conducted as a double-blind, crossover study. The formulas were applied to the faces of ten healthy, adult woman aged 21–67 previously tested and known to exhibit skin sensitivity to lactic acid. Prior to testing the abovedescribed two formulas, the volunteers' faces were washed with a standard, commercial beauty preparation, then gently patted dry. Approximately 1.0 mL of the two formulas was separately dispensed onto cotton swabs and liberally spread in smooth motions across the upper cheek area. Volunteers were instructed to record the discomfort/sting intensity of the two formulas after 2.5 and 5 minutes using the scale of Table 5. Additionally, the volunteers recorded all physical sensations. Relevant discomfort responses include: burning, stinging, tingling, itching, drying, smarting, prickly, and warm/hot. The evaluation method followed that described in Frosch, P.J. and Kligman, A.M., "A method for appraising the stinging capacity of topically applied substances," *J. Soc Cos Chem*, 28, p. 197-209 (1977), which hereby is incorporated in its entirety by reference.

[00144] In its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. The mean numerical scale rating for the first formula was 0.68, and the mean numerical scale rating for the second formula (with lightly- to moderately-crosslinked PVP) was 0.18 (Table 6). Seven of the women did not sense any discomfort or irritation from the second formula (with lightly- to moderately-crosslinked PVP).

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Table 5: Discomfort/sting intensity scale used in Example 10

numerical scale rating	volunteer perception
0	none
0.5	barely perceptible
1.0	slightly perceptible
1.5	definitely perceptible
2.0	moderately perceptible
2.5	dramatically perceptible
3.0	severely perceptible

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[00145] Table 6: Numerical scale rating results for the independent, third-part evaluation of Example 10.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	1.0	0.5	0	0	0
2	0.5	0.5	0.5	0	0	0
3	1.0	0	0.5	0.5	0	0.25
4	0	1.0	0.5	0	0	0
5	1.0	0	0.5	1.0	0.5	0.75
6	1.0	1.0	1.0	0	0	0
7	1.0	0.5	0.75	0	0	0
8	1.0	1.0	1.0	0	1.5	0.75
9	1.0	0	0.5	0	0	0
10	1.0	1.0	1.0	0	0	0
		mean:	**0.68**			**0.18**
		standard deviation:	**0.24**			**0.32**

Example 11: Reduced sting with salicylic acid solution

[00146] Example 10 was repeated except salicylic acid replaced tartaric acid in both formula 1, the control (without lightly- to moderately-crosslinked PVP) and formula 2, the composition of the invention (with lightly- to moderately-crosslinked PVP). The concentration of salicylic acid in Example 11 was 0.5% (w/w) in both solutions.

[00147] In its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. Less discomfort/sting and a more uniform volunteer perception was recorded by the volunteers for the

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formula of the example containing lightly- to moderately-crosslinked PVP (Table 7). Nine women did not sense any discomfort or irritation from the second formula (example of the invention).

[00148] Table 7: Numerical scale rating results for the independent, third-part evaluation of Example 11.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	0	0	0	0	0
2	1.0	1.0	1.0	0	0	0
3	1.0	1.0	1.0	0	0	0
4	1.0	1.0	1.0	0	0	0
5	0	0	0	0.5	0.5	0.5
6	1.5	1.0	1.25	0	0	0
7	1.0	0	0.5	0	0	0
8	1.0	1.0	1.0	0	0	0
9	1.0	1.0	1.0	0	0	0
10	0	1.0	0.5	0.5	0	0
		mean:	**0.72**			**0.075**
		standard deviation:	**0.45**			**0.16**

Example 12: Reduced sting with salicylic acid solution

[00149] Example 11 was repeated except a 2.0% salicylic acid solution replaced the 0.5% salicylic acid solution in both the control (without lightly- to moderately-crosslinked PVP) and the composition of the invention (with lightly- to moderately-crosslinked PVP).

[00150] Again, in its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. Less

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discomfort/sting and a more uniform volunteer perception was recorded by the volunteers for the formula of the example containing lightly- to moderately-crosslinked PVP (Table 8).

[00151] Table 8: Numerical scale rating results for the independent, third-part evaluation of Example 12.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	1.0	0.5	0	0	0
2	1.0	1.5	1.25	0	0	0
3	0	0	0	0.5	0	0.25
4	0	0	0	0	0.5	0.25
5	1.0	1.0	1.0	0	0.5	0.25
6	0.5	1.0	0.75	0	0	0
7	0	0	0	0	1.0	0.5
8	1.5	1.0	1.25	0	1.0	0.5
9	1.0	1.0	1.0	0	0	0
10	0	0	0	0.5	0.5	0.5
		mean:	**0.58**			**0.22**
	standard deviation:		**0.54**			**0.22**

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What is claimed is:

1. A composition comprising at least: (A) one personal care acid at 0.5% (% w/w) addition level or more, or one pharmaceutical acid at 0.5% (% w/w) addition level or more, and (B) lightly- to moderately-crosslinked PVP.

2. The composition of claim 1 wherein said addition level of either said personal care acid or said pharmaceutical acid is 1% or more.

3. The composition of claim 1 that has a pH of about 4 or lower.

4. The composition of claim 3 wherein said pH is about 2 or lower.

5. The composition of claim 1 that is a prescriptive or non-prescriptive composition.

6. The composition of claim 5 wherein said non-prescriptive composition is a personal care composition.

7. The composition of claim 1 that is applied on the skin, hair, scalp, foot, or lip of a mammal.

8. The composition of claim 5 that is an anti-aging composition, a composition for skin blemishes, a smoothing composition, a moisturizing composition, a skin firming composition, a skin lightening composition, an age-spot composition, a shampoo, or a cream for use around the eyes or mouth.

9. The composition of claim 1 wherein said personal care acid or pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N'*-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid

(procysteine), pyruvic acid, trichloroacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

10. The composition of claim 9 wherein hydroxy acid is selected from the group consisting of: alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

11. The composition of claim 9 wherein the said alpha hydroxy acid is selected from the group consisting of: alpha hydroxyethanoic acid, alpha hydroxyoctanoic acid, alpha hydroxycaprylic acid, ascorbic acid, adipic acid, caprylic acid, capric acid, glycolic acid, lactic acid, lauric acid, mandelic acid, mixed fruit acids, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, ricinoleic acid, oleic acid, tartaric acid, elaidic acid, erucic acid, and blends thereof.

12. The composition of claim 9 wherein the said beta hydroxy acid is selected from the group consisting of: beta hydroxybutanoic acid, tropic acid, trethocanic acid, salicylic acid, 5-(*n*-octanoyl) salicylic acid, and blends thereof.

13. The composition of claim 9 wherein said alpha and beta hydroxy acid is selected from the group of consisting of: citric acid, malic acid, tartaric acid, and blends thereof.

14. The composition of claim 9 wherein said polyhydroxy acid is selected from the group consisting of: gluconolactone acid, gactobionic acid, and blends thereof.

15. The composition of claim 1 having from about 0.1% to about 10% lightly- to moderately-crosslinked PVP.

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16. The composition of claim 1 having the form of: a solution, a cream, an ointment, a lotion, an oil-in-water emulsion, a water-in-oil emulsion, a shampoo, a spray, a gel, an aerosol, a suspension, a paste, a powder, a serum, or a mousse.

17. The composition of claim 1 that further comprises at least one additional ingredient selected from the group consisting of: active ingredients, emollients, liquid carriers, surfactants, emulsifiers, rheology modifiers, lubricants, diluents, humectants, anti-oxidants, preservatives, antibiotics, and blends thereof.

18. The composition of claim 17 further wherein said liquid carrier is selected from the group consisting of: water, alcohols, oils, esters, and blends thereof.

19. The composition of claim 1 having enhanced viscosity, enhanced viscosity stability, or enhanced viscosity and pH stability compared to the same composition without said lightly- to moderately-crosslinked PVP.

20. The composition of claim 1 having a Brookfield viscosity at 10 rpm of about 7,000 cP or more.

21. The use of a composition comprising at least: (A) one personal care acid at 0.5% addition level or more or one pharmaceutical acid at 0.5% addition level or more, and (B) lightly- to moderately-crosslinked PVP to deliver either said acid to the skin, scalp, foot, or lip of a mammal.

22. The use of claim 21 wherein said personal care acid or said pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N'*-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

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23. The use of claim 22 wherein said hydroxy acid is selected from the group consisting of: alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

24. The use of claim 21 wherein said addition level of either said personal care acid or said pharmaceutical acid is 1% or more.

25. The use of lightly- to moderately-crosslinked PVP in combination with at least one personal care acid or at least one pharmaceutical acid to reduce irritation, stinging, burning, tingling, itching, drying, smarting, prickly, and/or warm/hot perception on the skin, scalp, foot, or lip compared to the same composition not having said lightly- to moderately-crosslinked PVP.

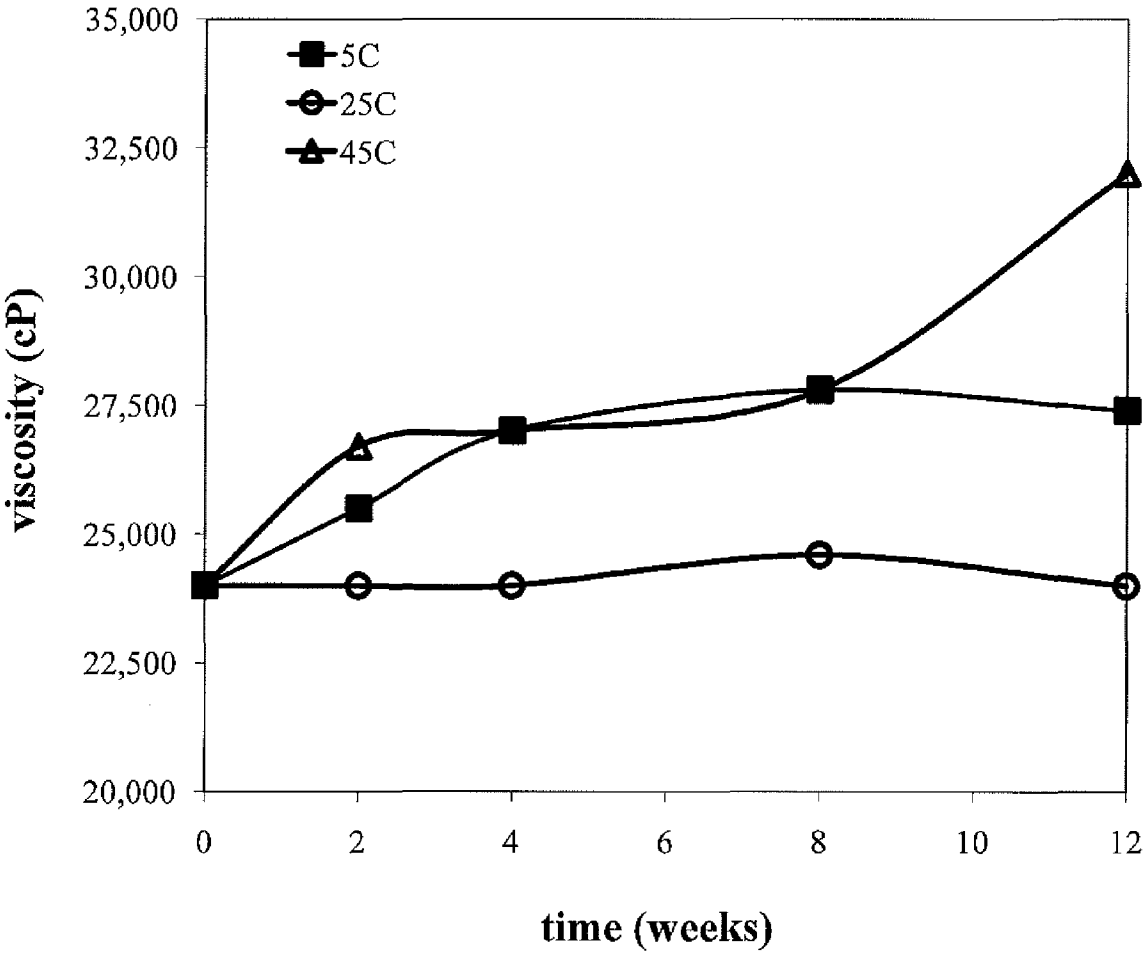

Fig: 1

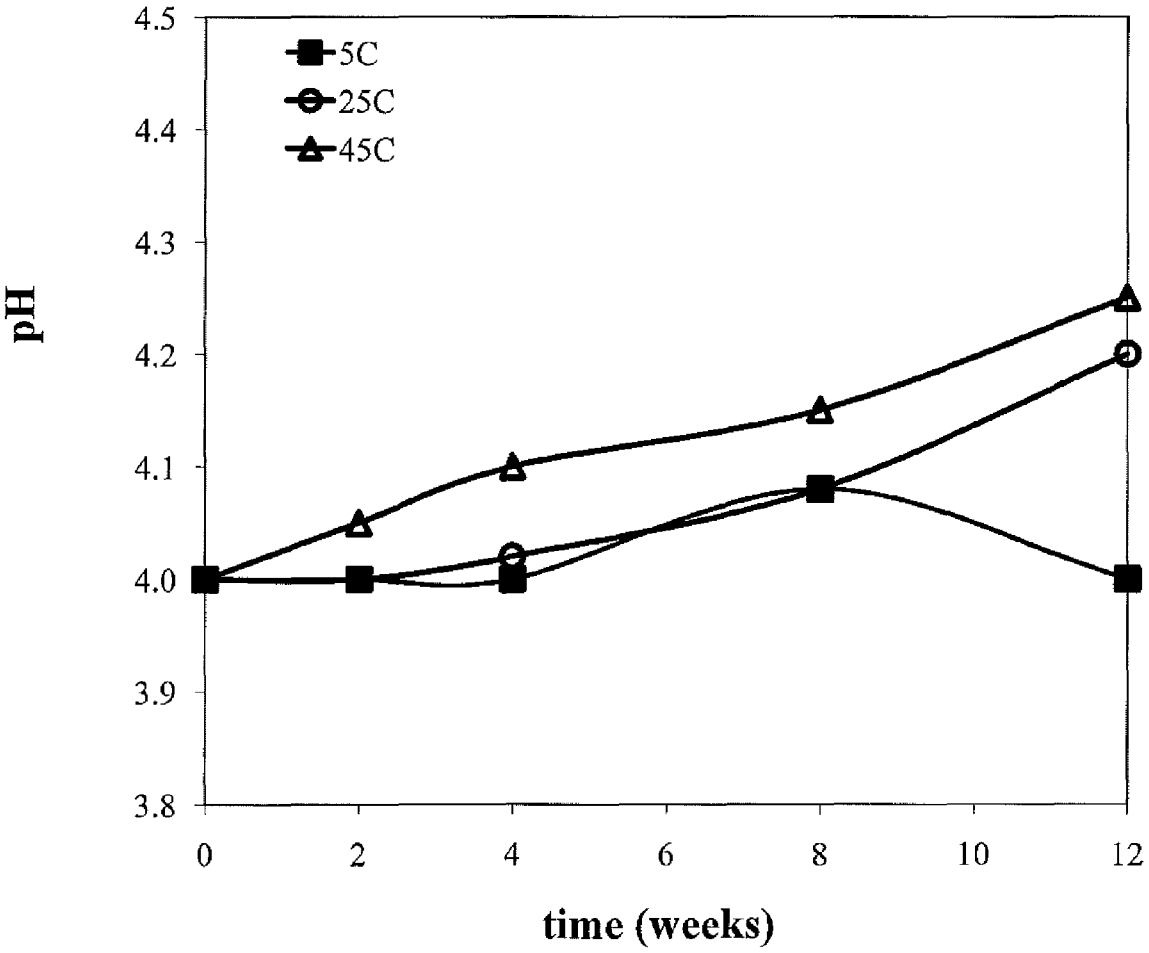

Fig: 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26976

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 8/02 (2010.01)
USPC - 424/401
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8) - A61K 8/02 (2010.01)
USPC - 424/401

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/401,400,59,65,66,68 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: lightly to moderately crosslinked PVP, hydroxy acid, pH, polyhydroxy, gluconolactone, gactobionic, irritation, viscosity, Brookfield

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,312,714 B1 (Prosise et al.) 6 November 2001 (06.11.2001), abstract, col 1, ln 13-50; col 4, ln 36-45; col 5, ln 27-30; col 6, ln 37-60; col 7, ln 10-14; col 12, ln 10-15; col 15, ln 39-41;	1-13, 15-25 --- 14
Y	US 2008/0113037 A1 (Green et al.) 15 May 2008 (15.05.2008), abstract, para [0011], [0012], [0045]	14
A	US 5,736,128 A (Chaudhuri et al.) 7 April 1998 (07.04.1998), entire disclosure	1-25
A	US 5,073,614 A (Shih et al.), 17 December 1991 (17.12.1991), entire disclosure	1-25
A	US 2004/0234491 A1 (Brautigam et al.) 25 November 2004 (25.11.2004), entire disclosure, esp: para [0046]	20

☐ Further documents are listed in the continuation of Box C. ☐

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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**** CONTINUING DATA ***************************

This application is a DIV of 14/082,955 11/18/2013 PAT 9161926
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**** FOREIGN APPLICATIONS ***************************

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Foreign Priority claimed	☐ Yes ☑ No	☐ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☐ Yes ☑ No		CA	3	10	2
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ADDRESS

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UNITED STATES

TITLE

TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

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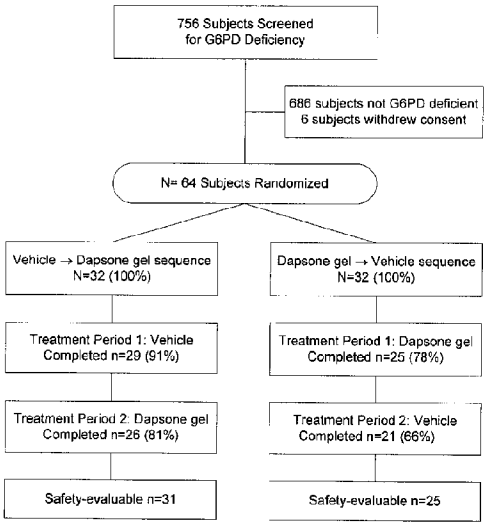
— *with international search report*

(54) Title: TOPICAL TREATMENT WITH DAPSONE IN G6PD-DEFICIENT PATIENTS

Figure 1



(57) Abstract: The present invention provides a pharmaceutical carrier system comprising a dermatological composition that is a semi-solid aqueous gel, wherein dapsone is dissolved in the gel such that the dapsone has the capacity to cross the stratum corneum layer of the epidermis, and wherein the composition also contains dapsone in a microparticulate state that does not readily cross the stratum corneum of the epidermis. The present invention also discloses the treatment of dermatological conditions in G6PD-def icient patients with the composition, while avoiding adverse hematologic effects.

WO 2009/061298 A1

TOPICAL TREATMENT WITH DAPSONE IN G6PD-DEFICIENT PATIENTS

Background of the Invention

Dapsone is a sulfone with both anti-inflammatory and antimicrobial properties. The oral formulation of the drug is used to treat leprosy, dermatitis herpetiformis, and malaria, using typical doses of 100 mg to 300 mg daily, but historically, it was also used to treat severe acne in doses ranging from 50 mg/day to 300 mg/week (Wolf et al., 2002; Ross 1961; Prendiville et al., 1988). Currently, use of oral dapsone is generally limited to more severe forms of skin disease, as its use may be associated with hematologic side effects, including hemolysis and hemolytic anemia that are dose-dependent and occur more frequently with increasing dose (Zhu and Stiller 2001; Jollow et al., 1995).

The mechanism of dapsone-related hemolysis and hemolytic anemia involves oxidative damage to red blood cells and is associated with the dapsone hydroxylamine metabolite (Prendiville et al., 1988). Red blood cells are somewhat protected against oxidative injury and lysis by glutathione reduction, a metabolic pathway that involves the glucose-6-phosphate dehydrogenase (G6PD) enzyme. Consequently, individuals who are G6PD-deficient are more sensitive to developing hemolytic anemia after exposure to hemolytic stressors such as infection, administration of a variety of drugs, including dapsone, or ingestion of fava beans (Beutler 1994). G6PD deficiency is most prevalent in individuals of African, Southeast Asian, and Middle Eastern heritage, and because the G6PD enzyme is encoded on the X chromosome, the deficiency is more common in males. In the United States, a recent study of military personnel reported the prevalence of G6PD deficiency to be 2.5% in men and 1.6% in women (Chinevere et al., 2006). Amongst racial groups, the prevalence was highest in African American men (12.2%), Asian men (4.3%), and African American women (4.1%), and lowest in Caucasian men and women (0.3% and zero, respectively). An early study that compared the effects of oral dapsone treatment in G6PD-deficient and non-deficient men found that there was a direct, linear relationship between oral dapsone dose and extent of red blood cell

hemolysis in both the normal and deficient groups. The doses causing hemolysis in G6PD-deficient subjects were approximately half of the doses that caused hemolysis in subjects with normal G6PD levels (DeGowin et al., 1966).

What is needed is a method of treating dermatological conditions in patients including G6PD-deficient patients without the adverse hematologic effects associated with oral dapsone administration.

Summary of the Invention

The present invention provides methods to treat glucose-6-phosphate dehydrogenase-deficient patients with dapsone. In one embodiment, the treatment is directed to dermatological conditions and the treatment is provided by a topical dapsone composition. The composition may include dissolved dapsone and microparticulate dapsone. In certain embodiments, the dermatological condition to be treated is inflammatory acne, non-inflammatory acne or rosacea.

Second medical uses of the dapsone composition and methods of manufacture using the dapsone composition for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient are also contemplated by the present invention.

The present invention provides a pharmaceutical carrier system comprising a dermatological composition that is a semi-solid aqueous gel, wherein dapsone is dissolved in the gel such that the dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically, and wherein the composition also contains dapsone in a microparticulate state that does not readily cross the stratum corneum of the epidermis. The ratio of microparticulate to dissolved dapsone is adjustable, but is preferably five or less. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In some embodiments, the dermatological composition for use in methods of treating glucose-6-phosphate dehydrogenase-deficient patients includes a thickening agent; water; a high-boiling, nonionic organic solvent; a

preservative; dapsone in a microparticulate and dissolved state; and a base solution. In one preferred embodiment, the composition includes about 0.5% to 4.0% carbomer; about 53.8% to 84.2% water; about 10% to 30% ethoxydiglycol; about 0.2% methylparaben; about 5% to 10% dapsone in a microparticulate and dissolved state; and about 0.1% to 2% sodium hydroxide solution. In some embodiments, the composition includes about 1% carbomer; about 81.8% water; about 10% ethoxydiglycol; about 0.2% methylparaben; about 5% dapsone in a microparticulate and dissolved state; and about 2% sodium hydroxide solution. In another preferred embodiment, the dermatological composition includes about 0.85% carbomer; about 66.95% water; about 25% diethylene glycol monoethyl ether; about 0.2% methylparaben; about 5% dapsone; and about 0.2% sodium hydroxide. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In certain embodiments, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying topically a dermatological gel composition that includes a semisolid aqueous gel; dapsone dissolved in the gel, wherein the dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically; and a microparticulate dapsone dispersed in the gel, wherein the microparticulate dapsone does not cross the stratum corneum of the epidermis in its microparticulate state. The dermatological condition can include inflammatory acne, non-inflammatory acne and/or rosacea.

In embodiments where acne is treated, the acne can be non-inflammatory acne, inflammatory acne, or both. In some embodiments, the dermatological dapsone composition is a semisolid aqueous gel. In other embodiments, the dermatological dapsone composition is a cream or a lotion. In still other embodiments, the dapsone composition is a suspension, ointment, or spray. In each of these embodiments, the dapsone may exist as a microparticulate form, a dissolved form, or both.

In a preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the

dermatological composition includes dapsone, wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone below the levels associated with hemolysis. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone between about 0.5μg/mL and 1.0 μg/mL. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone of about 1 μg/mL or less. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In another preferred embodiment, the invention provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by applying a dermatological composition to the condition, wherein the dermatological composition includes dapsone, and wherein the method results in blood plasma levels of dapsone between 0 and about 37 ng/mL and blood plasma levels of N-acetyl dapsone between 0 and about 50 ng/mL. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a

glucose-6-phosphate dehydrogenase-deficient patient using the dermatological composition are also contemplated by the present invention.

In some embodiments, the method of treating a G6PD-deficient patient with dapsone results in blood plasma levels of dapsone less than about 37 ng/mL and blood plasma levels of N-acetyl dapsone less than about 50 ng/mL. In some preferred embodiments, the method of treatment does not induce hemolytic anemia. In some preferred embodiments, the methods do not induce adverse hematologic events. In still further embodiments, the method is performed for about 12 weeks.

The invention also provides a method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient by topically applying a gel composition of dissolved dapsone and microparticulate dapsone, wherein the dissolved dapsone crosses the stratum corneum of the epidermis and is absorbed into the lower two-thirds of the pilosebaceous unit, and the microparticulate dapsone is primarily delivered into the upper third of the pilosebaceous unit, crossing the stratum corneum of the epidermis only minimally. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient using the gel composition are also contemplated by the present invention.

The use of a dermatological composition comprising about 0.85% carbomer; about 66.95% water; about 25% ethoxydiglycol; about 0.2% methylparaben; about 5% dapsone in a microparticulate and dissolved state; and about 0.2% sodium hydroxide solution, for the manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient, is also contemplated by the invention.

In a preferred embodiment, the invention also provides a method to treat a dermatological condition in a patient by topically applying a dermatological composition including dapsone, wherein the dermatological composition is formulated to result in blood plasma levels of dapsone of less than 1 microgram per mL in the patient. In some embodiments, the patient is predisposed to hemolytic anemia. In some embodiments, the method results in blood plasma levels of dapsone less than about 37 ng/mL and blood plasma levels of N-acetyl dapsone less than about 50 ng/mL. In still further embodiments, the

dermatological composition is a dermatological gel composition of a semisolid aqueous gel; dapsone dissolved in the gel, wherein the dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically; and a microparticulate dapsone dispersed in said gel, wherein the microparticulate dapsone does not cross the stratum corneum of the epidermis in its microparticulate state. Second medical uses of the dermatological composition and methods of manufacture of a medicament for treating dermatological conditions in patients using the gel composition are also contemplated by the present invention.

Methods for preparing the compositions of the present invention are also described.

Brief Description of the Figures

Figure 1. Study subject disposition. G6PD=glucose-6-phosphate dehydrogenase.

Figure 2. Correlation analysis of the change in hemoglobin versus change in bilirubin at week 2 of dapsone gel treatment (r^2=0.104; n=52). The mean bilirubin level was 0.58 mg/dL at baseline and 0.65 mg/dL at week 2. The mean change from baseline in bilirubin at week 2 (95% confidence limits) was +0.06 mg/dL (0 mg/dL, 0.12 mg/dL) (Patient data was collected in SI units and converted to conventional units for summary tables. To convert bilirubin mg/dL to SI units of μmol/L, multiply by 17.1). SI units= Systéme International units.

Figure 3. Correlation analysis of the change in hemoglobin versus change in reticulocytes at week 2 of dapsone gel treatment (r^2=0.043; n=52). The mean reticulocyte level was 1.30% at baseline and 1.51% at week 2. The mean change from baseline in reticulocyte level at week 2 (95% confidence limits) was +0.22% (0.11%, 0.32%).

Figure 4. Correlation analysis of the change in hemoglobin versus change in haptoglobin at week 2 of dapsone gel treatment (r^2=0.027; n=51). The mean haptoglobin level was 107.9 mg/dL at baseline and 109.1 mg/dL at week 2. The mean change from baseline in haptoglobin at week 2 (95% confidence limits) was –0.2 mg/dL (–5.3 mg/dL, 5.0 mg/dL) (Patient data was collected in SI units and converted to conventional units for summary tables. To convert

haptoglobin mg/dL to SI units of g/L, multiply by 0.01). SI units= Systéme International units.

Figure 5. Correlation analysis of the change in hemoglobin versus change in lactate dehydrogenase (LDH) at week 2 of dapsone gel treatment (r^2<0.001; n=51). The mean LDH level was 175.0 IU/L at baseline and 171.3 IU/L at week 2. The mean change from baseline in LDH at week 2 (95% confidence limits) was –3.3 IU/L (–10.0 IU/L, 3.4 IU/L).

Detailed Description of the Invention

Definitions

As used herein, "adverse event" means any adverse change in health or "side-effect" that occurs in a patient who is participating in a study while the patient is receiving treatment (dermatological composition or vehicle) or within a pre-specified period of time after their treatment has been completed.

As used herein, "cream" refers to an emulsified medicinal or cosmetic preparation; a semisolid emulsion of either the oil-in-water or the water-in-oil type, ordinarily intended for topical use.

As used herein, "dapsone" refers to the chemical compound dapsone having the chemical formula $C_{12}H_{12}N_2O_2S$ as well as bis(4-aminophenyl)sulfone, 4',4'-diaminodiphenyl sulfone and its hydrates, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, diaphenylsulfone, dapsone analogs, and dapsone related compounds. "Dapsone analogs" refers to chemical compounds that have similar chemical structures and thus similar therapeutic potential to dapsone such as the substituted bis(4-aminophenyl)-sulfones. "Dapsone related compounds" refers to chemical compounds that have similar therapeutic potential, but are not as closely related by chemical structure to dapsone such as the substituted 2,4-diamino-5-benzylpyrimidines.

A "foam" refers to a mass of bubbles of air or other gas entrapped in a matrix of liquid or solid, especially an accumulation of fine, frothy bubbles formed in or on the surface of a liquid or solid, as from agitation or generated under pressure of a gas.

As used herein, the terms "G6PD-deficient" or "G6PD deficiency" refer to glucose-6-phosphate dehydrogenase (G6PD) levels that are below 7 U/g Hb,

which is considered to be the lower limit of normal. As used herein, ≤2 U/g Hb is considered "severely" deficient.

As used herein, "gel" refers to a colloid in a more solid form than a solution; a jelly-like material formed by the coagulation of a colloidal liquid; many gels have a fibrous matrix and fluid filled interstices: gels are viscoelastic rather than simply viscous and can resist some mechanical stress without deformation.

As used herein, the term "microparticulate" refers to any solid form of an active agent, including dapsone, that is not dissolved in the dermatological composition. The microparticulate dapsone described herein may be in the form of flakes or crystals, and includes a precipitant that results from the addition of water and the solvent or mixed solvent system containing dapsone. The microparticulate dapsone may comprise a crystalline precipitant or an amorphous precipitant.

As used herein, "ointment" refers to a salve or unguent for application to the skin, specifically a semisolid medicinal preparation usually having a base of fatty or greasy material; an ointment has an oil base whereas a cream is water-soluble. See, The University of Newcastle Dept. of Medical Oncology On-Line Medical Dictionary (http://cancerweb.ncl.ac.uk/omd/) December 19, 2003 and MedLine Plus Medical Dictionary (http://www.nlm.nih.gov/medlineplus/mplusdictionary.html) December 19, 2003.

The term "topical" as used herein refers to the route of administration of a dermatological composition that involves direct application to the body part being treated, e.g., the skin. Examples of topical application include application to the skin of creams, lotions, gels, ointments or other semisolids to rub-on, solutions to spray, or liquids to be applied by an applicator. Rinse-off application with washes, cleansers, or shampoos are also examples of topical application. Typically, areas of the body suitable for application of the dermatological composition include the skin of the face, throat, neck, scalp, chest, back, ears, and other skin sites where dermatological conditions may occur.

As used herein, the term "treat", "treatment", or "treating" refers to the reduction in number and/or severity of symptoms, including individual skin

lesions; prevention of the development of symptoms, including skin lesions; or global improvement in the appearance of symptoms, including skin lesions.

The invention described herein is directed to methods of treating dermatological disorders in G6PD-deficient patients through use of a topical dapsone formulation. Aczone™ gel, 5%, a topical formulation of dapsone, was developed to deliver therapeutic concentrations of dapsone to the skin. The United States Food and Drug Administration (US FDA) approved Aczone™ gel, 5%, for the treatment of acne vulgaris, but required certain language in the package insert due to the US FDA's concern that this drug carries a significant risk of serious hematological adverse effects, including hemolysis, in G6PD-deficient patients.

The US FDA required that the Aczone™ gel, 5%, label state that all patients should be screened for G6PD deficiency prior to initiation of Aczone™ treatment, with routine monitoring of complete blood counts and reticulocyte counts during treatment with Aczone™ in those patients identified as having a history of anemia and predisposition to increased hemolytic effect with dapsone (e.g., G6PD deficiency). While previous clinical studies did not demonstrate evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin level were noted to be associated in a G6PD deficient patient treated with Aczone™ gel, 5% for acne vulgaris.

The methods and compositions of the invention described herein demonstrate the unexpected result that treatment of G6PD-deficient patients with the Aczone™ gel, 5%, formulation does not result in adverse hematological effects.

Dapsone

Dapsone was first synthesized in 1908 and has been used medically as an antibiotic and an anti-inflammatory. Dapsone is a bis(4-aminophenyl)sulfone also known as 4',4'-diaminodiphenyl sulfone, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, and diaphenylsulfone. Dapsone has been used orally for the treatment of acne (Ross 1961) and been found to have a minimum inhibitory concentration with regard to *P. acnes* of about 1 microgram per milliliter (Godowski et al., 2000).

Dapsone analogs and related compounds have been described in U.S. Pat. Nos. 4,829,058 and 4,912,112 to Seydel et al. The '058 patent discloses substituted bis(4-aminophenyl)sulfones useful for inhibiting growth of bacteria, mycobacteria, and plasmodia. Some of these compounds were also tested against dapsone for toxicity and anti-inflammatory activity (Coleman et al., 1996a). In the '112 patent, substituted 2,4-diamino-5-benzyl pyrimidines having antimicrobial activity particularly against mycobacteria are described. Some of these compounds were also tested against dapsone for toxicity (Coleman et al., 1996b) and anti-inflammatory activity (Coleman et al., 1997). The teachings of these references in combination with subsequent publications showed that these analogs and related compounds have activity similar to dapsone and would be expected to have similar treatment efficacy.

Topical Dapsone Compositions

The present invention comprises compositions for application to the skin of G6PD-deficient patients. The compositions comprise microparticulate dapsone precipitates in adjustable ratios of microparticulate to dissolved dapsone. The invention also comprises methods for preparation of the compositions, and methods for treatment of skin conditions in G6PD-deficient patients using the compositions. The advantages of the present invention are appreciated in the treatment of skin conditions or diseases by using topical dapsone, thus minimizing the hematologic effects associated with oral dapsone treatment. The present invention is particularly effective in the treatment of acne. Because of the nature of the microparticulate dapsone in the composition, microparticulate dapsone will be retained in or above the stratum corneum and will therefore serve as a reservoir or provide drug action in the supracorneum zone. The dissolved dapsone will pass through the stratum corneum.

Topical dapsone formulations have been described in U.S. Pat. No. 5,733,572 to Unger et al., and U.S. Pat. Nos. 6,056,954; 6,056,955; 6,254,866; 6,248,324; and 6,277,399 to Fischetti et al. A topical composition including dapsone for acne treatment has been described in U.S. Pat. Nos. 5,863,560, and 6,060,085 to Osborne which are herein incorporated by reference in their entirety.

Clinical studies have shown that dapsone gel, 5% (Aczone™; QLT USA, Inc. Fort Collins, Colorado) (dapsone gel), is effective in the treatment of acne vulgaris (Draelos et al., 2007) and results in ≤1% of the systemic exposure that is seen with typical oral dapsone treatment (Thiboutot et al., 2007).

Dapsone Topical Gel. In a preferred embodiment, a dermatological condition in a G6PD-deficient patient is treated by topically applying a dermatological composition that is part of a novel pharmaceutical carrier system of a semisolid aqueous gel, wherein the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum to become systemically available, and microparticulate dapsone that is retained in or above the stratum corneum to serve as a reservoir or to provide dapsone to the supracorneum zone. The microparticulate dapsone may comprise a crystalline precipitant or an amorphous precipitant.

Optimal balance is accomplished by having a semisolid gel carrier system in which microparticulate dapsone precipitates are formed in reproducible ratios with respect to the dissolved dapsone. For the composition to have a wide range of applicability, the microparticulate to dissolved dapsone ratio preferably should be no greater than five, at therapeutic levels of applied active dapsone.

A composition having a microparticulate to dissolved dapsone ratio of less than two may provide the greatest amount of pharmaceutical available for immediate partition out of the stratum corneum and into the viable epidermis. This should provide minimum reservoir capacity, but may not maintain sustained delivery or provide maximum activity in the supracorneum zone. A composition having a microparticulate to dissolved dapsone ratio of two or greater may have a reduced amount of drug available for immediate partition out of the stratum corneum and into the viable epidermis. This provides maximum reservoir capacity, and maintains sustained delivery, providing maximum activity in the supracorneum zone. In an example of a dermatological composition of this inventive method, the ratio for microparticulate dapsone to dissolved dapsone should be no greater than 50, preferably no greater than 10, and most preferably no greater than 5. Drug delivery from the microparticulate/dissolved dapsone formulation may be optimized to provide higher levels of drug to the supracorneum zone, while maintaining the level of

drug partitioning out of the stratum corneum and into the viable epidermis, despite 10-fold increases in the amount of pharmaceutical applied to the skin.

Thickening agents include polymer thickeners. Polymer thickeners that may be used include those known to one skilled in the art, such as hydrophilic and hydroalcoholic gelling agents frequently used in the cosmetic and pharmaceutical industries. Preferably, the hydrophilic or hydroalcoholic gelling agent comprises "CARBOPOL®" (B. F. Goodrich, Cleveland, Ohio), "HYPAN®" (Kingston Technologies, Dayton, N.J.), "NATROSOL®" (Aqualon, Wilmington, Del.), "KLUCEL®" (Aqualon, Wilmington, Del.), or "STABILEZE®" (ISP Technologies, Wayne, N.J.). Preferably, the gelling agent comprises between about 0.2% to about 4% by weight of the composition. More particularly, the preferred compositional weight percent range for "CARBOPOL®" is between about 0.5% to about 2%, while the preferred weight percent range for "NATROSOL®" and "KLUCEL®" is between about 0.5% to about 4%. The preferred compositional weight percent range for both "HYPAN®" and "STABILEZE®" is between about 0.5% to about 4%.

"CARBOPOL®" is one of numerous cross-linked acrylic acid polymers that are given the general adopted name carbomer. These polymers dissolve in water and form a clear or slightly hazy gel upon neutralization with a caustic material such as sodium hydroxide, potassium hydroxide, triethanolamine, or other amine bases. "KLUCEL®" is a cellulose polymer that is dispersed in water and forms a uniform gel upon complete hydration. Other preferred gelling polymers include hydroxyethylcellulose, hydroxypropylcellulose, cellulose gum, MVA/MA copolymers, MVE/MA decadiene crosspolymer, PVM/MA copolymer, or a combination thereof.

Preservatives may also be used in this dermatological composition and preferably comprise about 0.05% to 0.5% by weight of the total composition. The use of preservatives assures that if the product is microbially contaminated, the formulation will prevent or diminish microorganism growth. Some preservatives useful in this invention include methylparaben, propylparaben, butylparaben, chloroxylenol, sodium benzoate, DMDM Hydantoin, 3-Iodo-2-Propylbutyl carbamate, potassium sorbate, chlorhexidine digluconate, or a combination thereof.

Titanium dioxide may be used as a sunscreen to serve as prophylaxis against photosensitization. Alternative sunscreens include methyl cinnamate. Moreover, BHA may be used as an antioxidant, as well as to protect ethoxydiglycol and/or dapsone from discoloration due to oxidation. An alternate antioxidant is BHT.

In one embodiment, the dermatological composition that is applied comprises a semi-solid or gel-like vehicle that may include a polymer thickener, water, preservatives, active surfactants or emulsifiers, antioxidants, sunscreens, and a solvent or mixed solvent system.

In a preferred embodiment, the dermatological composition includes a thickening agent; water; a high-boiling, nonionic organic solvent; a preservative; dapsone in a microparticulate and dissolved state; and a base solution. Ethoxydigylcol and 1-methyl-2-pyrollidone are preferred solvents for use in the topically applied dermatological composition. Sodium hydroxide is a preferred base for use in the topically applied dermatological composition. The solvent or mixed solvent system is important to the formation of the microparticulate to dissolved dapsone ratio. The formation of the microparticulate, however, should not interfere with the ability of the polymer thickener or preservative systems to perform their functions.

In one embodiment, the dermatological composition includes about 0.5% to 4.0% carbomer and about 0.5% to 10% dapsone that exists in both a dissolved state and a microparticulate state. In some embodiments, the dermatological composition comprises about 1% carbomer, about 80-90% water, about 10% ethoxydiglycol, about 0.2% methylparaben, and about 0.3% to 5.0% dapsone including both microparticulate dapsone and dissolved dapsone, and about 2% caustic base material. More particularly, the carbomer may include "CARBOPOL® 980" and the caustic base material may include sodium hydroxide solution.

In a preferred embodiment, the composition comprises dapsone and ethoxydiglycol, which allows for an optimized ratio of microparticulate drug to dissolved drug. This ratio determines the amount of drug delivered, compared to the amount of drug retained in or above the stratum corneum to function in the supracorneum domain. The system of dapsone and ethoxydiglycol may include purified water combined with "CARBOPOL®" gelling polymer, methylparaben,

propylparaben, titanium dioxide, BHA, and a caustic material to neutralize the "CARBOPOL®"

In one embodiment, the dermatological composition that is applied comprises about 0.5% to 4.0% carbomer; about 73.8 to 82.3% water; about 10% ethoxydiglycol; about 0.2% methylparaben; about 5% to 10% dapsone in a microparticulate and dissolved state; and about 2% to sodium hydroxide solution. In another embodiment, the dermatological composition comprises about 1% carbomer; about 81.8% water; about 10% ethoxydiglycol; about 0.2% methylparaben; about 5% dapsone in a microparticulate and dissolved state; and about 2% sodium hydroxide solution. In one preferred embodiment, the composition comprises about 0.5% to 4.0% carbomer; about 53.8% to 84.2% water; about 10% to 30% ethoxydiglycol; about 0.2% methylparaben; about 5% to 10% dapsone in a microparticulate and dissolved state; and about 0.1% to 2% sodium hydroxide solution.

In a more preferred embodiment, the dermatological composition that is applied comprises about 0.85% carbomer, about 66.95% water, about 25% diethylene glycol monoethyl ether (i.e., ethoxydiglycol), about 0.2% methylparaben, about 5% dapsone, and about 0.2% sodium hydroxide solution.

Dapsone Topical Cream or Lotion. In another embodiment, dapsone may be applied as a topical cream or lotion in which dapsone is dissolved or dispersed or both partially dissolved and partially dispersed. Topical creams or lotions may be either oil-in-water emulsions or water-in-oil emulsions. The oil phase may include but is not limited to fatty alcohols, acids, or esters such as cetyl palmitate, cetyl alcohol, stearyl alcohol, stearic acid, isopropyl stearate, glycerol stearate, mineral oil, white petrolatum, or other oils alone or in combination.

Emulsifiers that may be added to the composition include, but are not limited to, steareth 20, ceteth 20, sorbitan sesquioleate, sorbitan mono-oleate, propylene glycol stearate, dosium lauroyl sarcosinate, polysorbate 60, or combinations. Preservatives, antioxidants, fragrances, colorants, sunscreens, thickeners, and other additives required to achieve pharmaceutical or cosmetically acceptable or preferred product may also be included. However, topical creams and lotions are not limited to these components since one skilled

in the art will be aware of additional components useful in the formulation of topical creams and lotions.

Dapsone Topical Solution or Suspension. In another embodiment, dapsone may be applied as a solution or suspension. These are fluid solvent or mixed-solvent systems including, but not limited to, water, ethanol, propylene glycol, glycerol, polyethylene glycol, ethyl acetate, propylene carbonate, n-methyl pyrolidone, triethanolamine, 1,4-butanediol, triacetin, diacetin, dimethyl isosorbide alone or in combination. Preservatives, antioxidants, fragrances, colorants, sunscreens, thickeners, suspending agents, enhancers, and other additives required to achieve pharmaceutically or cosmetically acceptable or preferred product may also be included. Again, topical solutions or suspensions are not limited to these components, since one skilled in the art will be aware of additional components useful in the formulation of topical solutions or suspensions.

Other Dapsone Topical Formulations. Dapsone may also be applied using a pharmaceutical or cosmetic carrier form such as an ointment, roll-on or stick product, micro-emulsion, shake powder, an aerosolized spray or mousse, a pump spray or mousse, or bath additive. Examples of ointments include essentially non-aqueous mixtures of petrolatum, lanolin, polyethylene glycol, plant or animal oils, either hydrogenated or otherwise chemically modified. An ointment may also contain a solvent in which dapsone is either fully or partially dissolved. Additional pharmaceutical carriers will be known to those skilled in the art and this list should not be considered to be limiting.

Method for Preparing the Dapsone Dermatological Composition

The present invention also provides methods for preparing the dermatological compositions described above. In a general form, the method for producing a dermatological gel composition having dissolved dapsone and microparticulate dapsone precipitates comprises the steps of completely dissolving dapsone in a solvent or solvent mixture; adding and adequately dispersing a polymeric thickener in water; and combining the dissolved dapsone with the dispersed polymeric thickener. Alternatively, water may be slowly added to the dissolved dapsone, followed by the addition of a polymeric

thickener. Ethoxydigylcol and 1-methyl-2-pyrollidone are preferred solvents for use in the topically applied dermatological composition.

In one preferred embodiment, the method for preparing a topically applied dermatological composition having dissolved and microparticulate dapsone comprises the steps of forming a homogenous dispersion by stirring purified water vigorously enough to form a vortex and sifting gel polymer into the vortex formed in the water while continuing to stir; forming a pharmaceutical component by dissolving methyl paraben and/or propylparaben in ethoxydiglycol by mixing to form a solution, and mixing dapsone with the solution until the pharmaceutical is dissolved; mixing the pharmaceutical component with the homogenous dispersion to form a microparticulate dapsone dispersion; and adding a caustic material.

In a preferred embodiment, the method for preparing the topically applied dermatological composition having dissolved and microparticulate dapsone comprises the following steps: a polymer thickener component is prepared by charging 66.95 grams of purified water to a vessel suitable to contain 100 grams of finished semisolid product, and slowly sifting 0.85 g of "CARBOPOL® 980" into a vortex formed by rapidly stirring the purified water. When a homogeneous dispersion of "CARBOPOL® 980" and water is formed, stirring is reduced to minimize air entrapment. Next, an active pharmaceutical component is prepared by charging an appropriately sized container with 25 g of ethoxydiglycol, then 0.2 g of methylparaben are added to the ethoxydiglycol and mixed until all of the crystalline solid is dissolved. 5.0 g dapsone is added to the ethoxydiglycol and mixed until the drug is completely dissolved. The polymer thickener component is added to the pharmaceutical component with mixing, immediately resulting in the formation of crystalline microparticles. Once the dispersion is homogenous, 2.0 grams of a 10% w/w aqueous sodium hydroxide solution are added to neutralize the CARBOPOL® 980 and form the gel.

The order in which reagents are combined may be important, depending on the particular reagents necessary for the target mixture. For example, after a pharmaceutical such as dapsone is dissolved in a solvent such as ethoxydiglycol, water may be slowly added to the dapsone in the ethoxydiglycol solution, or the dapsone in ethoxydiglycol solution may be added to the water with mixing. Adding the dapsone in ethoxydiglycol solution to water may result in less

polydispersity in the size of the microparticulates than adding water to the dapsone in ethoxydiglycol solutions. The carbomer is generally dispersed in the water component of the formulation, while the remaining ingredients will be dissolved or dispersed in whichever of the two components are best for dissolving or dispersing the ingredient. For example, it is suggested to dissolve methylparaben, propylparaben, and BHA in ethoxydiglycol. After the ethoxydiglycol component and water component are combined, neutralizer is added to formulate the gel.

The compositions of the present invention may further comprise other optional ingredients that may modify the physical, chemical, cosmetic or aesthetic characteristics of the compositions. The compositions may also further comprise optional inert ingredients. Many such optional ingredients are known for use in topical, including anti-acne compositions, and may also be used in the topical compositions herein, provided that such optional materials are compatible with the essential materials described herein, or do not otherwise unduly impair product performance.

The relative percentages for each of the reagents used in the present invention may vary depending upon the desired strength of the target formulation, gel viscosity, and the desired ratio of microparticulate to dissolved dapsone. Unless otherwise designated, all reagents listed above are commonly known by one of ordinary skill in the art and are commercially available from pharmaceutical or cosmetic excipient suppliers.

Dermatological conditions

The methods described herein treat dermatological conditions in G6PD-deficient patients by the topical application of a dermatologic composition comprising dapsone. In a preferred embodiment, acne conditions, e.g., inflammatory acne lesions and non-inflammatory acne lesions, are treated. In other embodiments, rosacea is treated.

Acne. Acne is chronic pilosebaceous unit inflammation associated with the face and trunk, usually occurring in adolescence due to complex interactions of androgens and bacteria. For the adolescent, circulating androgen results in significantly increased sebum production. The sebaceous glands dramatically enlarge and excrete more sebum than the immature pilosebaceous canals can

accommodate. The follicular canal contains keratinous material, i.e., dead skin cells, from the wall of the canal, sebum from the sebaceous glands, and bacteria, predominately *Propionibacterium acnes*. The *P. acnes* feed upon the sebum, converting triglycerides to fatty acids, and dramatically increase in number due to an increase in volume of the nutrition source. The increase in constricted immature ducts and bacterial waste products results in plugged follicles and subsequent typical acne inflammation.

When the follicular canal becomes blocked, a comedone is formed. The primary manifestation of non-inflammatory acne is the closed comedone, which are small, circumscribed, elevated lesions of the follicle that are often without a visible central plug. Closed comedones (whiteheads) are non-inflammatory acne lesions. Open comedones (blackheads) consist of small follicular lesions having a central black keratin plug as a result of oxidation of melanin pigment. Open comedones develop from closed comedones as the orifice dilates. The open comedone is not an inflammatory lesion unless traumatized, i.e. picked at, by the patient. Comedones, either open or closed, are non-inflammatory. While the comedone is the primary lesion of acne, comedones are not unique to acne since they may be seen in other conditions such as senile comedones or trophic skin resulting from x-ray therapy.

Closed comedones are potential precursors to large inflammatory lesions. The dead skin cells of the comedone are permeated with lipid and *P. acnes*, and as the follicle dilates from the expanding mass of keratin and lipid, inflammation develops along the follicular wall. This can lead to follicular wall rupture which extrudes the entire contents of the comedone into the dermis, generating a greater inflammatory response. Inflammatory lesions can be small papules with an encircling inflammatory region or, depending on the site and extent of the rupture, a pustule or large tender nodule may form. Papules, pustules and nodules are the three clinical descriptions for inflammatory acne.

As summarized by Strauss (J. S. Strauss. (1991). "Biology of the Sebaceous Gland and Pathophysiology of Acne Vulgaris," Chapter 13 in Pathophysiology of Dermatologic Diseases, Second Edition. N. A. Sotor and H. Baden eds., McGraw-Hill, New York: pp. 195-210) there are four principles of acne therapy: 1) correct the pattern of altered keratinization within the follicle; 2) decrease sebaceous gland activity; 3) decrease the *P. acnes* population and/or

decrease the generation of inflammatory substances by the bacterial population; and 4) produce non-inflammatory effects.

Topical retinoids such as tretinoin primarily function by correcting altered patterns of keratinization. Oral isotretinoin (13-cis retinoic acid) primarily functions by decreasing sebaceous gland activity. Known antibiotic therapies such as oral minocycline or topical clindamycin primarily function by reducing the numbers or activity of *P. acnes*.

Acne is one condition where a highly specialized topical drug delivery is needed. Ideally, a topical active agent would be primarily delivered into the pilosebaceous unit, with only minimal active crossing of the skin barrier. Intact stratum corneum lines the upper third of the pilosebaceous unit, and it is into this upper third of the hair follicle that the sebaceous duct secretes sebum. Thus, a need exists for an acne treatment that maximizes drug levels in the upper third of the pilosebaceous unit.

Additionally, when an active agent is used to treat acne, it is important to increase the level of drug that will cross the intact stratum corneum lining the upper third of the pilosebaceous unit. By definition, inflammation is the response of the viable epidermis to irritants and sensitizers. In order to reduce the amount of inflammation, the active pharmaceutical must penetrate past the stratum corneum and interfere with the cascade of inflammatory events. Ideally, delivery of an anti-inflammatory for acne requires that steady-state levels be sustained. The delivery system described herein provides dapsone above the stratum corneum and below the stratum corneum.

In one preferred embodiment of the invention, a method for treating acne in G6PD-deficient patients is employed by topically applying dapsone. Specifically, the invention includes a method for reducing the number of inflammatory acne lesions in G6PD-deficient patients by topically applying a dermatological composition comprising dapsone. The invention also includes a method for reducing the number of non-inflammatory acne lesions in G6PD-deficient patients by topically applying a dermatological composition comprising dapsone. Furthermore, in another embodiment, a method is provided for topically applying a dermatological composition comprising dapsone to prevent closed comedones (non-inflammatory acne) from becoming inflamed papules,

pustules, or nodules in G6PD-deficient patients. However, if the follicular canal ruptures, dapsone would also help to reduce the resultant inflammation.

Rosacea. Rosacea is estimated to affect over 45 million people worldwide. Early stages of rosacea are characterized by erythema (flushing and redness) on the central face and across the cheeks, nose, or forehead but can also less commonly affect the neck and chest. As rosacea progresses, erythema, telangiectasia (dilation of superficial blood vessels on the face), red domed papules (small bumps) and pustules, red gritty eyes, burning and stinging sensations, and in some advanced cases, a red lobulated nose (rhinophyma) develop. The disorder can co-exist with acne vulgaris and/or seborrheic dermatitis.

There are four identified rosacea subtypes (Wilkin et al., 2004) and patients may have more than one subtype present. First, erythematotelangiectatic rosacea is characterized by permanent redness (erythema) with a tendency to flush and blush easily. It is also common to have small blood vessels visible near the surface of the skin (telangiectasias) and possibly burning or itching sensations. Second, papulopustular rosacea is characterized by some permanent redness with red bumps (papules) with some pus filled (pustules) (which typically last 1-4 days). Third, phymatous rosacea is most commonly associated with rhinophyma, an enlargement of the nose. Symptoms include thickening skin, irregular surface nodularities, and enlargement. Phymatous rosacea can also affect the chin (gnatophyma), forehead (metophyma), cheeks, eyelids (blepharophyma), and ears (otophyma; Jansen and Plewig 1998). Small blood vessels visible near the surface of the skin (telangiectasias) may be present. Fourth, ocular rosacea is characterized by red, dry and irritated eyes and eyelids. Some other symptoms include foreign body sensations, itching and burning.

Rosacea may be triggered by episodes of skin flushing and blushing. Exposure to temperature extremes, strenuous exercise, heat from sunlight, severe sunburn, stress, anxiety, cold wind, moving to a warm or hot environment from a cold one, and foods and drinks containing alcohol, caffeine, histamines, spices, and antioxidants, can trigger flushing and blushing that contribute to the development of rosacea.

Other Dermatological Conditions. In other embodiments of the invention, a topical dapsone formulation is used to treat G6PD-deficient patients suffering from impetigo, erythrasma, erysipelas, rosacea (perioral dermatitis, rhinophyma), furuncles, carbuncles, alopecia, panniculitis, psoriasis, dermatitis, cysts, bullous diseases (pemphigus vulgaris, bullous pemphigoid, and herpes gestationis), collagen vascular diseases (dermatomyositis, systemic lupus erythematosus, eosinophilic fasciitis, relapsing polychondritis, and vasculitis), sarcoidosis, Sweet's disease, lichen planus, hirsutism, toxic epidermal necrolysis, dermatitis herpetiformis, eczema, atopic dermatitis, seborrhoeic dermatitis (dandruff, cradle cap), diaper rash, urushiol-induced contact dermatitis, erythroderma, lichen simplex chronicus, prurigo nodularis, itch, pruritus ani, nummular dermatitis, dyshidrosis, pityriasis alba, parapsoriasis (pityriasis lichenoides et varioliformis acuta, pityriasis lichenoides chronica), pityriasis rosea, pityriasis rubra pilaris, urticaria (dermatographic urticaria, cholinergic urticaria), erythema (erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema annulare centrifugum, erythema marginatum), sunburn, actinic keratosis, polymorphous light eruption, radiodermatitis, erythema ab igne, nail disease, onychogryposis, Beau's lines, yellow nail syndrome, follicular disorders, alopecia areata (alopecia universalis), androgenic alopecia, telogen effluvium, lichen planopilaris, trichorrhexis nodosa, hypertrichosis (hirsutism), epidermoid cysts, sebaceous cysts, pseudofolliculitis barbae, hidradenitis suppurativa, miliaria, anhidrosis, body odor, chromhidrosis, vitiligo, melasma, freckles, café au lait spots, lentigo/liver spots, seborrheic keratosis, acanthosis nigricans, callus, pyoderma gangrenosum, bedsores, keloids, granuloma annulare, necrobiosis lipoidica, granuloma faciale, morphea, calcinosis cutis, sclerodactyly, ainhum or livedoid vasculitis.

While the dermatological conditions described herein serve as examples of how therapeutic approaches can require dramatically different drug delivery profiles, all skin diseases are best treated by a particular drug delivery strategy tailored specifically to the pharmaceutical and the particular disease. Some diseases are best treated using pulsed or spiked delivery in which high levels of drug are delivered in a short period of time. This type of treatment saturates receptor sites and provides maximum microbial or viral replication inhibition,

thus providing optimal therapy for certain diseases. Conversely, a cosmetic, topical, or transdermal product that provides steady state active pharmaceutical delivery while minimizing excipient delivery provides the preferred skin delivery profile for other diseases. Thus, the carrier system described herein, which can be adjusted to optimize the delivery profile for the pharmacology of the active drug and the nature of the disease state, advances the effectiveness of pharmaceutical products applied to the skin of G6PD-deficient patients.

The dapsone dermatological composition is typically applied to affected skin once or twice daily, but may be applied more frequently, depending on the severity of the condition. Hence, application may be as often as 3, or 4, or 5, or 6 times during a day, or even more. Typically, for most persons affected with acne, application once or twice during a day is sufficient.

The initial dosage, including frequency of the topical application and the length of the initial treatment period, can be determined depending on the specific type of dermatological condition, severity of the disease, and the response of the patient to the medication. The application should be repeated on a regular basis for at least 2 weeks in some embodiments, for at least 3 weeks in some embodiments, for at least 4 weeks in some embodiments, for at least 5 weeks in some embodiments, for at least 6 weeks in some embodiments, for at least 7 weeks in some embodiments, for at least 8 weeks in some embodiments, for at least 9 weeks in some embodiments, for at least 10 weeks in some embodiments, for at least 11 weeks in some embodiments, for at least 12 weeks in some embodiments, or longer in some embodiments. After elimination or reduction of the symptoms of the dermatological condition, application may be continued, or may be reduced to fewer times a day and/or fewer days a week to maintain the condition of the skin.

The dermatological compositions described herein can be sold as a kit wherein the composition is packaged in a container, such as a plastic container. Written instructions on how to use the dermatological composition in accordance with the present invention are included on or associated with the container, which provides instructions for treating dermatological conditions in G6PD-deficient patients.

The invention will be further described by reference to the following detailed, non-limiting examples.

Example 1

Hematologic Safety of Dapsone Topical Gel, 5%

Methods

Study Design. The study was a double-blind, randomized, vehicle-controlled, crossover, post-approval commitment study. Subjects were equally randomized into 1 of 2 sequences of treatment according to a computer-generated randomization scheme: dapsone gel followed by vehicle gel or vehicle gel followed by dapsone gel. The vehicle gel consisted of the same inactive ingredients as the dapsone gel. After washing with a standard, nonmedicated cleanser (Cetaphil, Galderma Laboratories, LP), subjects applied a thin film of the study treatment twice daily (once in the morning and once at night) to the entire face and, as required, to acne-affected areas of the neck, shoulders, upper chest, and upper back. Subjects applied each treatment for a period of 12 weeks, with a 2-week washout period between treatments and a 2-week follow-up period following the last treatment, for a total study duration of 28 weeks.

Study Treatment. The method for preparing the topically applied dermatological composition having dissolved and microparticulate dapsone comprised the following steps: a polymer thickener component was prepared by charging 66.95 grams of purified water to a vessel suitable to contain 100 grams of finished semisolid product, and slowly sifting 0.85 g of "CARBOPOL® 980" into a vortex formed by rapidly stirring the purified water. When a homogeneous dispersion of "CARBOPOL® 980" and water was formed, stirring was reduced to minimize air entrapment. Next, an active pharmaceutical component was prepared by charging an appropriately sized container with 25 g of ethoxydiglycol, then 0.2 g of methylparaben were added to the ethoxydiglycol and mixed until all of the crystalline solid was dissolved. 5.0 g dapsone was added to the ethoxydiglycol and mixed until the drug was completely dissolved. The polymer thickener component was added to the pharmaceutical component with mixing, immediately resulting in the formation of crystalline microparticles.

Once the dispersion was homogenous, 2.0 grams of a 10% w/w aqueous sodium hydroxide solution were added to neutralize the CARBOPOL® 980 and form the gel.

Subjects. The subjects were age ≥12 years, had a diagnosis of G6PD deficiency (defined as having G6PD enzyme activity below the lower limit of normal; refer to Laboratory and Safety Assessments below), and had a diagnosis of acne vulgaris (defined as having at least 20 inflammatory and/or noninflammatory lesions, with at least 10 lesions located on the face). Subjects were excluded if they had severe cystic acne or acne conglobata, had received treatment with isotretinoin within 3 months of baseline, or were using other topical and/or systemic medications for acne at the time of study entry. Subjects were also excluded if they had a predisposition to anemia for other medical reasons, such as gastrointestinal bleeding or cancer.

Laboratory and Safety Assessments. Adverse events were collected throughout the study with standard interviewing techniques at each study visit. Blood tests were scheduled for the baseline, 2-week, and 12-week time points of each treatment period to measure plasma dapsone and n-acetyl dapsone concentrations and evaluate clinical chemistry and hematology parameters. Lesion counts were assessed for efficacy at selected time points.

Blood samples from all subjects were tested for G6PD deficiency using a validated spectrophotometric assay performed with a commercially-available kit (Trinity Biotech PLC, Ireland). The laboratory's normal reference range for G6PD activity was 7.0 to 20.5 U/g Hb. Plasma dapsone and n-acetyl dapsone metabolite concentrations were measured by CANTEST BioPharma Services (Burnaby, British Columbia, Canada) using a validated liquid chromatography tandem mass spectrometry method. The lower limit of quantification for this assay was 0.30 ng/mL; levels below the lower limit of quantification were assigned a value of zero for the summary analyses. All clinical chemistry and hematology tests were analyzed centrally by Quintiles Laboratories (Smyrna, Georgia, USA), which assigned a high or low flag to any values that were determined to be outside of the laboratory normal range.

Statistical Methods. The intent-to-treat (ITT) population was defined as all randomized subjects, the safety population was defined as all subjects who applied dapsone gel or vehicle gel at least once, and the safety-evaluable population was defined as all subjects who applied at least 50% of the required treatment applications and had the Week 2 blood draw in the first treatment period. To assess the risk of hemolysis and hemolytic anemia, the following laboratory parameters were identified as important markers: hemoglobin, bilirubin, reticulocyte counts, haptoglobin, and lactate dehydrogenase (LDH). For each of these parameters, the values at each time point, changes from baseline at 2 and 12 weeks, and within-subject between-treatment differences in the values and changes from baseline were summarized with descriptive statistics (mean, standard deviation, median, minimum, and maximum). Two-sided 95% confidence intervals (CI) were also calculated for the changes from baseline and within-subject between-treatment differences in the change from baseline. In addition, the number and percentage of subjects with any of the following outcomes were determined for the 2-week and 12-week time point of each treatment period: a hemoglobin shift from normal or high to below normal or from low to normal or high; a hemoglobin reduction ≥1 g/dL; an increase in bilirubin above the upper limit of normal; an increase in reticulocyte count above the upper limit of normal; a reduction in haptoglobin below the lower limit of normal; and a ≥1 g/dL reduction in hemoglobin with concomitant increase in bilirubin, increase in reticulocytes, or reduction in haptoglobin. Unplanned correlation analyses between the changes in hemoglobin and changes in reticulocytes, bilirubin, haptoglobin, or LDH were performed with Pearson correlations. A preplanned subgroup analysis based on the degree of G6PD deficiency, which was defined as "severely deficient" (≤2 U/g Hb) and "deficient" (>2 U/g Hb up to the lower limit of normal at 7 U/g Hb) was performed for all variables related to the risk of hemolysis.

Results

Subject Disposition and Demographic Characteristics. A total of 756 subjects were screened for G6PD deficiency; 64 subjects (8.5%) were identified as G6PD-deficient and consented to participation (Figure 1). Of the 64 subjects in the intent-to-treat population, 63 comprise the safety population and 56

comprise the safety-evaluable population. Seventeen subjects did not complete the study, primarily for administrative reasons (loss to follow-up, voluntary withdrawal, treatment noncompliance, urticaria [not related to treatment], pre-existing anemia [protocol violation], pregnancy), but 1 of these subjects discontinued due to mild contact dermatitis.

Baseline demographics and characteristics were similar between treatment groups. The majority of subjects were African American (88%; 56/64) and the mean age of subjects was 28 years (Table 1). Six adolescent subjects (9%) were enrolled in the study (age <16 years). The mean of G6PD enzyme activity was 3.8 U/g Hb (range 0.7 to 6.9 U/g Hb). Fifteen subjects (23%) had severe G6PD-deficiency, defined as G6PD enzyme activity ≤2 U/g Hb, which represented the lower 30% of the below normal range; 14 of these subjects are included in the safety-evaluable population.

Table 1. Demographic and Baseline Characteristics (Intent-To-Treat)

Characteristic	
Total subjects, no.	64
Age, mean ± SD (range), y	28 ± 10 (12-61)
Women, no. (%)	35 (55)
Ethnic group, no. (%)	
African American	56 (88)
Asian	4 (6)
Hispanic	1 (2)
Other[a]	3 (5)
Glucose-6-phosphate dehydrogenase (G6PD) enzyme activity	
Mean ± SD (range), U/g Hb	3.8 ± 1.9 (0.7-6.9)
Severely deficient,[b] no. (%)	15 (23)
Deficient,[b] no. (%)	49 (77)
Inflammatory lesion count, no.	
Mean ± SD (range)	16.2 ± 12.5 (0-50)
Noninflammatory lesion count, no.	
Mean ± SD (range)	26.5 ± 25.4 (0-139)
Total lesion count,[c] no.	
Mean ± SD (range)	42.8 ± 27.8 (10-162)

SD=standard deviation

[a] The subjects who identified their ethnic group as "other" were Middle Eastern, mixed race (White + Black), and Haitian.

[b] Severely deficient is defined as ≤2 U/g Hb; deficient is defined as >2 U/g Hb up to the lower limit of normal at 7 U/g Hb

[c] Total lesion count is the sum of inflammatory and noninflammatory lesion counts.

Lesion Counts. Eficacy variables collected in this study were lesion counts (inflammatory, noninflammatory, and total). In all lesion categories,

Aczone™-treated subjects experienced larger absolute reductions in lesions than vehicle-treated subjects after 12 weeks in the first treatment period. There was a higher percentage reduction in inflammatory lesion counts in Aczone™-treated subjects than vehicle-treated subjects (44% compared with 29%). Non-inflammatory lesion counts decreased by 5% in the Aczone™ group.

This was a cross-over design study that enrolled subjects with a baseline lesion count of at least 20 (mean total lesion count was 42.8 lesions). The primary purpose of this study was to evaluate safety, and therefore no statistical tests were planned for comparisons of the efficacy variables. The lesion counts were lower at the baseline of the second treatment period compared with the first, which indicates that the clinical effects of treatment last longer than the 2-week washout period and therefore, the evaluation of changes in lesion counts in treatment period 2 is confounded by the use of treatment during treatment period 1. Because of this, it is most relevant to evaluate changes in lesion counts over the first treatment period only.

After the first 12 weeks of the study, subjects treated with Aczone™ experienced a 44% drop in inflammatory lesion counts and 5% drop in non-inflammatory lesion counts. This pattern is consistent with the results from the pivotal phase 3 studies, in which Aczone™ demonstrated a larger effect on inflammatory lesions than noninflammatory lesions. Comparing Aczone™ and vehicle treatments in other lesion categories, it was observed that vehicle treatment in this study resulted in a better reduction in non-inflammatory lesion counts while the percentage reduction in total lesion count was similar between Aczone™ and vehicle. However, the absolute reduction in lesion counts was numerically better with Aczone™ treatment for all lesion categories. This variability in lesion counts is not unexpected given the small sample size of the study.

Plasma Dapsone and Metabolite Concentrations. Dapsone and N-acetyl dapsone levels reached steady-state within 2 weeks of dapsone gel treatment and fell rapidly after the cessation of treatment. Mean plasma concentrations of dapsone were approximately 5 ng/mL at both 2 and 12 weeks of treatment, while mean plasma concentrations of n-acetyl dapsone were approximately 2.5 ng/mL at each time point (Table 2). In subjects who applied dapsone gel in the first

treatment period, dapsone levels were largely undetectable by the baseline of the vehicle treatment period and completely undetectable by Week 2 of vehicle treatment (n=25, median dapsone concentration was 0, maximum concentration was 1.18 ng/mL at Week 2).

Table 2. Plasma Concentrations of Dapsone and N-Acetyl Dapsone for Subjects Treated with Dapsone Gel, 5% (Safety Population)

		Dapsone (ng/mL)	N-Acetyl Dapsone (ng/mL)
2 Weeks	n	58	58
	Mean ± SD	5.626 ± 6.101	2.767 ± 6.750
	Range	0.00-36.85	0.00-48.70
12 Weeks	n	51	51
	Mean ± SD	5.295 ± 6.660	2.514 ± 4.792
	Range	0.00-30.58	0.00-26.88

SD=Standard deviation

Hemolysis-Related Laboratory Results. The primary hemolysis-related analysis was performed on the safety-evaluable data set (N=56). At 2 weeks of treatment, subjects treated with dapsone gel experienced a nominal mean decrease in hemoglobin from baseline of 0.32 g/dL (95% confidence limits –0.47 g/dL, –0.17 g/dL); no change from baseline was evident at 12 weeks of treatment (95% confidence limits –0.20 g/dL, 0.14 g/dL). In comparison, vehicle-treated subjects did not experience any changes in hemoglobin (Table 3). However, the within-subject between-treatment differences also show that subjects had hemoglobin values at 12 weeks of dapsone gel treatment that were similar to their level at 12 weeks of vehicle treatment.

The number of subjects who had a ≥1 g/dL hemoglobin decrease was similar between vehicle and dapsone gel treatment at Week 2 (4 subjects [7%] on vehicle compared with 6 subjects [11%] on dapsone gel). At Week 12, the number of subjects who had a ≥1 g/dL decrease was also similar between vehicle and dapsone gel treatment (4 subjects [7%] on vehicle with 2 subjects [4%] on

dapsone gel). In addition, the range of hemoglobin changes from baseline was similar between vehicle and dapsone gel treatments, with changes in both positive and negative directions observed at each time point. The largest decrease in hemoglobin observed during the study occurred during vehicle treatment (1.7 g/dL decrease at Week 2).

After 2 weeks, hemoglobin shifts below normal were seen in 3 of 55 subjects (5%) during vehicle treatment and 6 of 52 subjects (12%) during dapsone gel treatment (Table 3). However, for both treatment groups, all of the low hemoglobin values remained close to the normal range and none of these subjects were diagnosed clinically with anemia. After 12 weeks, 4 of 50 subjects (8%) on vehicle and 3 of 49 subjects (6%) on dapsone gel experienced a hemoglobin shift to below the lower limit of normal. Three subjects experienced a shift in hemoglobin to below normal during both the vehicle and the dapsone gel treatment periods.

Table 3. Hemoglobin Values, Changes from Baseline, and Shifts from Normal (Safety Evaluable Population)

Visit	Treatment Group: Vehicle gel	Treatment Group: Dapsone gel, 5%	Within-Subject Difference[a]
Pretreatment	**n=56**	**n=53**	**n=53**
Value, mean ± SD (g/dL)	13.36 ± 1.25	13.44 ± 1.34	–0.062 ± 0.593
2 Weeks	**n=55**	**n=53**	**n=52**
Value, mean ± SD (g/dL)	13.34 ± 1.25	13.12 ± 1.36	0.238 ± 0.696
Change from baseline, mean ± SD	0.01 ± 0.64	–0.32 ± 0.55	0.316 ± 0.957
Range	–1.7 to 1.4	–1.5 to 1.5	–2.4 to 2.5
95% confidence interval[b]	(–0.16, 0.18)	(–0.47, –0.17)	(0.047, 0.585)
≥1 g/dL drop, no./n (%)[c]	4/56 (7%)	6/56 (11%)	
Shift to below normal, no./n (%)[d]	3/55 (5%)	6/52 (12%)	
12 Weeks	**n=50**	**n=50**	**n=46**
Value (g/dL), mean ± SD	13.37 ± 1.38	13.42 ± 1.24	–0.024 ± 0.639
Change from baseline, mean ± SD	0.01 ± 0.64	–0.03 ± 0.59	0.044 ± 0.913
Range	–1.5 to 1.6	–1.5 to 1.4	–2.0 to 2.4
95% confidence interval[b]	(–0.18, 0.19)	(–0.20, 0.14)	(–0.230, 0.319)
≥1 g/dL drop, no./n (%)[c]	4/56 (7%)	2/56 (4%)	
Shift to below normal, no./n (%)[d]	4/50 (8%)	3/49 (6%)	

SD=standard deviation

[a] Difference is calculated as the vehicle value minus the dapsone gel value in the same subject

[b] Confidence intervals are for the change from baseline (pretreatment value)

[c] Denominators are the number of subjects at baseline

[d] Based on observed data

The changes in hemoglobin observed at week 2 were not correlated with plasma dapsone levels or grams per day of dapsone gel use (average use was 1 g/day). The changes in hemoglobin at week 2 were also not correlated with changes in bilirubin, reticulocytes, haptoglobin, or LDH (Figures 2 to 5). Correlation analyses showed that the regression lines between changes in bilirubin or haptoglobin and changes in hemoglobin slope in the opposite direction from those expected for hemolysis (ie, bilirubin would be expected to increase and haptoglobin would be expected to decrease in parallel with a decrease in hemoglobin) (Figures 2 and 4). No subjects experienced any concomitant changes of reticulocytes, haptoglobin, or LDH at 2 or 12 weeks of dapsone gel treatment. The various analyses of hemoglobin described above were similar between the safety evaluable and the safety populations of the study.

Two subjects experienced a change in hemoglobin of ≥ g/dL with a concomitant increase of bilirubin to above the upper limit of normal (1 subject at 2 weeks of dapsone gel treatment and the other subject at 12 weeks). Neither subject experienced any other laboratory changes, particularly in the sensitive hemolysis marker haptoglobin, or clinical signs of hemolytic anemia. In addition, the subject with the changes at week 12 had similarly high bilirubin levels at week 2 of dapsone gel treatment and at week 12 of vehicle gel treatment, with no concomitant change in hemoglobin at these time points.

Changes in hemoglobin and other hemolysis parameters were also examined in various subgroups including G6PD enzyme activity, race, gender, and age. All of these subgroups demonstrated a similar pattern of changes in laboratory parameters as described for the safety-evaluable population. In particular, subjects who were severely G6PD-deficient (≤ U/g Hb) did not appear to be at higher risk for changes in hemoglobin or other parameters (Table 4).

Table 4. Hemoglobin, Bilirubin, Reticulocyte, Haptoglobin, and Lactate Dehydrogenase Levels by Severity of G6PD Enzyme Activity

		G6PD Enzyme Activity[a]			
		Severely Deficient[b] (n=14)		Deficient[b] (n=42)	
Parameter	Visit	Vehicle gel	Dapsone gel, 5%	Vehicle gel	Dapsone gel, 5%
Hemoglobin (g/dL)[c]	Pretreatment	13.96 ± 0.80	13.97 ± 0.81	13.15 ± 1.32	13.25 ± 1.44
	2 Weeks	13.91 ± 0.98	13.65 ± 0.79	13.14 ± 1.28	12.93 ± 1.48
	12 Weeks	13.85 ± 0.85	13.86 ± 1.05	13.21 ± 1.50	13.24 ± 1.28
Bilirubin (mg/dL)[d]	Pretreatment	0.7 ± 0.3	0.7 ± 0.2	0.5 ± 0.3	0.5 ± 0.3
	2 Weeks	0.7 ± 0.3	0.8 ± 0.3	0.5 ± 0.2	0.6 ± 0.3
	12 Weeks	0.8 ± 0.3	0.7 ± 0.4	0.6 ± 0.4	0.5 ± 0.3
Reticulocytes (%)	Pretreatment	1.38 ± 0.42	1.29 ± 0.45	1.33 ± 0.63	1.31 ± 0.47
	2 Weeks	1.31 ± 0.44	1.59 ± 0.57	1.35 ± 0.55	1.48 ± 0.51
	12 Weeks	1.45 ± 0.48	1.38 ± 0.53	1.39 ± 0.59	1.53 ± 0.61
Haptoglobin (mg/dL)[e]	Pretreatment	93.57 ± 35.86	99.23 ± 30.13	118.10 ± 53.89	110.75 ± 48.17
	2 Weeks	107.86 ± 29.66	102.14 ± 42.82	117.00 ± 48.42	111.54 ± 42.15
	12 Weeks	95.38 ± 32.05	96.43 ± 30.54	117.03 ± 53.64	120.57 ± 50.11
Lactate dehydrogenase	Pretreatment	166.5 ± 34.5	162.0 ± 31.3	177.5 ± 38.9	179.6 ± 35.8

		G6PD Enzyme Activity[a]			
		Severely Deficient[b] (n=14)		Deficient[b] (n=42)	
Parameter	Visit	Vehicle gel	Dapsone gel, 5%	Vehicle gel	Dapsone gel, 5%
(IU/L)	2 Weeks	165.1 ± 40.1	169.2 ± 32.1	179.0 ± 38.3	172.1 ± 31.6
	12 Weeks	165.8 ± 33.4	174.1 ± 43.8	180.5 ± 36.8	177.1 ± 34.2

G6PD=glucose-6-phosphate dehydrogenase

[a] Value ± standard deviation

[b] Severely deficient is defined as ≤2 U/g Hb; deficient is defined as >2 U/g Hb up to the lower limit of normal at 7 U/g Hb

[c] Patient data was collected in Systéme International (SI) units and converted to conventional units for summary tables. To convert g/dL to SI units of g/L, multiply by 10

[d] To convert mg/dL to SI units of µmol/L, multiply by 17.1

[e] To convert mg/dL to SI units of g/L, multiply by 0.01

One subject with pre-existing anemia at baseline and 2 subjects with histories of anemia were treated during the study. The subject with pre-existing anemia was treated with dapsone gel for 9 days before being withdrawn. However, despite being anemic at the start of dapsone gel treatment, she did not experience any worsening of hemoglobin or changes in other parameters after 9 days of treatment. The 2 subjects with histories of anemia completed the study. There were no changes in chemistry or hematology parameters indicative of dapsone-related hemolysis in either of these subjects during the study.

Adverse Events. No adverse events were reported that were clinical signs or symptoms of hemolytic anemia. A total of 27 of 63 subjects (43%) in the full safety data set experienced an adverse event, regardless of relationship to treatment. Few adverse events were considered by the investigator to be related to dapsone gel treatment (17 events out of 44 events) and these occurred in only 8 of 63 subjects (13%): 7 during the dapsone gel treatment period and one during the vehicle treatment period. Four of these subjects reported local application site reactions of burning, dryness, pruritus, or contact dermatitis (all mild). The one event of contact dermatitis that led to discontinuation of study treatment was mild in intensity, did not require treatment, and resolved within 14 days of discontinuation. One subject reported a related adverse event of aggravated acne. Three subjects had related adverse events from a laboratory test result during treatment with dapsone gel, but none of these were indicative of hemolytic anemia: elevated bilirubin at 2 weeks and low hematocrit and low red blood cell count at 12 weeks in Subject 1; low haptoglobin at 2 weeks and RBC Burr cells, poikilocytosis, and elliptocytosis at 12 weeks in Subject 2; and low white blood cell count at week 12 in Subject 3. In Subject 1, the elevation in bilirubin occurred before the low hematocrit and RBC count and is therefore not believed to be indicative of hemolysis. In Subject 2, plasma dapsone levels were below the limit of quantification, even though treatment use could be verified by tube weights. Furthermore, the low haptoglobin was present at the baseline blood test as well as week 12, and no other changes in the other hematology parameters occurred, so the laboratory adverse events for this subject are likely not related to dapsone gel treatment. For Subject 3, no laboratory or clinical

evidence of hemolysis or hemolytic anemia accompanied the low white blood cell count.

Discussion

This study was designed specifically to evaluate the risk of hemolytic anemia with dapsone gel treatment in subjects with G6PD deficiency, which is a population at higher risk of drug-induced hematologic effects. The study employed a crossover design to evaluate both dapsone gel and vehicle treatments within the same subject. To evaluate hemolysis, subjects were monitored for changes in hemolysis-related laboratory parameters of hemoglobin, reticulocytes, haptoglobin, bilirubin, and LDH at 2 and 12 weeks of each treatment. Because drug-induced hemolytic anemia is a relatively acute phenomenon, the 2-week time point was determined to be the most relevant for observing any laboratory evidence of hemolysis or hemolytic anemia, while the 12-week time point would allow evaluation of any longer-term changes (Dern et al., 1954). Adverse events were also evaluated to determine if there were any clinical signs of hemolytic anemia.

An evaluation of the laboratory data showed a mean decrease in hemoglobin from baseline of 0.32 g/dL after 2 weeks of dapsone gel treatment, which was not seen at 12 weeks even as treatment continued. For several reasons, the nominal decrease in hemoglobin at Week 2 was considered to be clinically insignificant. First, there were no mean changes from baseline in other laboratory markers of hemolysis at either the 2-week or 12-week time point, nor any relationship between changes in hemoglobin and these parameters, including bilirubin, haptoglobin, reticulocytes, and LDH. These findings strongly argue against the presence of clinically relevant hemolysis. Second, no subjects experienced symptoms of or were diagnosed clinically with hemolytic anemia. No therapeutic interventions or modifications to study treatment were required as a consequence of a laboratory finding, even for subjects who experienced the largest decreases of hemoglobin (–1.7 g/dL and –1.5 g/dL for vehicle and dapsone gel treatment, respectively). Third, there was no consistent, clinically meaningful relationship between changes in hemoglobin and dapsone gel treatment. The range of hemoglobin changes and percentages of subjects with shifts below normal or large decreases of hemoglobin ($\geq$ g/dL) were similar

between vehicle and dapsone gel treatments. Some subjects experienced changes in hemoglobin during both treatments, and some subjects had very low or unmeasurable plasma levels of dapsone.

This study also provides substantive data on a subgroup of 14 subjects whose G6PD levels were severely deficient, within the lower 30% of the G6PD-deficient range (≤ 2 U/g Hb). Results in this subgroup were consistent with the overall population and support that there is no difference in risk of hemolysis after dapsone gel treatment in G6PD-deficient subjects with the lowest enzyme activity. In addition, 1 subject with pre-existing anemia and 2 subjects with histories of anemia participated in the study. The subject with pre-existing anemia was withdrawn from the study after 9 days of treatment, but the other 2 subjects completed the full 28 weeks of the study. None of these 3 subjects experienced any changes in chemistry and hematology parameters indicative of dapsone-related hemolysis.

Because the G6PD enzyme is encoded on the X chromosome, the deficiency is generally more common in males, and the prevalence of G6PD deficiency in African-American men can be almost 3 times higher than that of African-American women (Chinevere et al., 2006). However, in this study, the ratio of males to females with G6PD deficiency was almost equal, with 55% (35/64) of eligible subjects being female. It could be speculated that because almost 60% of individuals who present at dermatologists' offices for skin concerns are female (Fleischer et al., 1994), and at least 41% of women will have acne at various times in their lives (Poli et al., 2001), investigators were able to identify a large number of female patients with both G6PD deficiency and acne. Subgroup analyses of all variables related to assessing the risk of hemolysis based on gender showed no differences between females and males, and the results for each subgroup were similar to the overall safety evaluable population.

Plasma dapsone and N-acetyl dapsone levels were measured pre-treatment and at the 2-week and 12-week time points of each treatment period to assess systemic exposure. To obtain a level of treatment exposure that was relevant to topical dapsone gel use in a real-world setting, subjects were instructed to apply treatment to the entire face twice-daily, and they could also apply treatment to other acne-affected areas of the neck, shoulders, upper chest, and/or upper back at their discretion. Dapsone and N-acetyl dapsone levels

reached steady state within 2 weeks of treatment with dapsone gel, and fell rapidly after the cessation of treatment. Systemic exposure to dapsone after topical dapsone gel treatment was low, considering both the mean (approximately 5 ng/mL) and the maximum exposure in the study (approximately 37 ng/mL) (Table 2). The level of dapsone exposure observed in this study is substantially lower than the levels associated with oral dosing that would be expected to cause hematologic changes (DeGowin 1967). Hemolysis associated with oral dapsone use is a dose-dependent effect (Zhu and Stiller 2001; Jollow et al., 1995). We did not observe any correlation between plasma dapsone levels or grams of dapsone gel use and changes in hemoglobin, likely because systemic dapsone exposure was at the very low end of the dose-relationship observed with oral dapsone treatment. Pharmacokinetic modeling indicates that steady-state systemic dapsone levels after topical dapsone gel treatment would still be approximately 35-fold (C_{max}) to 63-fold (AUC) lower than the systemic levels of dapsone following a single 50 mg oral dose.

The results from this study demonstrate that there are no clinically significant effects on chemistry and hematology parameters or clinical signs of hemolytic anemia in G6PD-deficient subjects following treatment of acne vulgaris with dapsone gel. Because G6PD deficiency represents a highly sensitive marker for the hemolytic potential of drugs, this finding can be extrapolated to all acne patients with normal G6PD enzyme activity. Data from this study confirm that the safety profile for topical dapsone gel treatment is excellent, and support that the risk of hemolytic anemia during treatment with dapsone gel for acne vulgaris is remote for all patients, including those with G6PD deficiency.

All of the publications cited hereinabove are incorporated by reference herein. The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

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WHAT IS CLAIMED IS:

1. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying a dermatological composition to said condition, wherein said dermatological composition comprises dapsone.

2. The method of claim 1, wherein the dermatological composition comprises dissolved dapsone and microparticulate dapsone.

3. The method of claim 1, wherein the dermatological condition is selected from the group consisting of inflammatory acne, non-inflammatory acne and rosacea.

4. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying topically a dermatological gel composition including microparticulate pharmaceutical and dissolved pharmaceutical, which comprises:

a thickening agent;
water;
a high-boiling, nonionic organic solvent;
a preservative;
dapsone in a microparticulate and dissolved state;
and a base solution.

5. The method of claim 4, comprising:
about 0.5% to 4.0% carbomer;
about 53.8% to 84.2% water;
about 10% to 30% ethoxydiglycol;
about 0.2% methylparaben;
about 5% to 10% dapsone in a microparticulate and dissolved state;
and about 0.1 to 2% sodium hydroxide solution.

6. The method of claim 5, comprising:
about 0.85% carbomer;
about 66.95% water;
about 25% ethoxydiglycol;
about 0.2% methylparaben;
about 5% dapsone in a microparticulate and dissolved state;
and about 0.2% sodium hydroxide solution.

7. The method of claim 4, wherein the ratio of microparticulate to dissolved dapsone is no greater than 5.

8. The method of claim 4, wherein the dermatological condition is selected from the group consisting of inflammatory acne, non-inflammatory acne and rosacea.

9. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying topically a dermatological gel composition comprising:
a semisolid aqueous gel;

dapsone dissolved in said gel, wherein said dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically; and

a microparticulate dapsone dispersed in said gel, wherein said microparticulate dapsone does not cross the stratum corneum of the epidermis in its microparticulate state.

10. The method of claim 9, wherein the dermatological condition is selected from the group consisting of inflammatory acne, non-inflammatory acne and rosacea.

11. A method to treat acne in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying topically a dermatological composition comprising dapsone.

12. The method of claim 11, wherein the acne is non-inflammatory acne.

13. The method of claim 11, wherein the acne is inflammatory acne.

14. The method of claim 11, wherein the dermatological composition is selected from the group consisting of a semisolid aqueous gel, a cream, a lotion, a suspension, an ointment and a spray.

15. The method of claim 11, wherein the dermatological composition comprises dissolved dapsone and microparticulate dapsone.

16. The method of claim 1, wherein the method results in blood plasma levels of dapsone less than about 37 ng/mL and blood plasma levels of N-acetyl dapsone less than about 50 ng/mL.

17. The method of claim 1, wherein the method does not induce hemolytic anemia.

18. The method of claim 1, wherein the method does not induce adverse hematologic events.

19. The method of claim 1, wherein the method is performed for about 12 weeks.

20. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying a dermatological composition to said condition, wherein said dermatological composition comprises dapsone, wherein the method results in blood plasma levels of dapsone between 0 and about 37 ng/mL and blood plasma levels of N-acetyl dapsone between 0 and about 50 ng/mL.

21. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising topically applying a gel composition comprising dissolved dapsone and microparticulate dapsone, wherein:

the dissolved dapsone crosses the stratum corneum of the epidermis and is absorbed into the lower two-thirds of the pilosebaceous unit; and

the microparticulate dapsone is primarily delivered into the upper third of the pilosebaceous unit, crossing the stratum corneum of the epidermis only minimally.

22. A method to treat a dermatological condition in a glucose-6-phosphate dehydrogenase-deficient patient comprising applying a dermatological composition to said condition, wherein said dermatological composition comprises dapsone, wherein the method results in blood plasma levels of dapsone and N-acetyl dapsone below the levels associated with hemolysis.

23. The use of a dermatological composition comprising about 0.85% carbomer; about 66.95% water; about 25% ethoxydiglycol; about 0.2% methylparaben; about 5% dapsone in a microparticulate and dissolved state; and about 0.2% sodium hydroxide solution, for the manufacture of a medicament for treating dermatological conditions in a glucose-6-phosphate dehydrogenase-deficient patient.

24. A method to treat a dermatological condition in a patient comprising topically applying a dermatological composition comprising dapsone, wherein the dermatological composition is formulated to result in blood plasma levels of dapsone of less than 1 microgram per mL in the patient.

25. The method of claim 24, wherein the patient is predisposed to hematologic side effects including hemolysis and/or hemolytic anemia.

26. The method of claim 24, wherein the method results in blood plasma levels of dapsone less than about 37 ng/mL and blood plasma levels of N-acetyl dapsone less than about 50 ng/mL.

27. The method of claim 24, wherein the dermatological composition is a dermatological gel composition comprising

a semisolid aqueous gel;

dapsone dissolved in said gel, wherein said dapsone has the capacity to cross the stratum corneum layer of the epidermis and become available systemically; and

a microparticulate dapsone dispersed in said gel, wherein said microparticulate dapsone does not cross the stratum corneum of the epidermis in its microparticulate state.

Figure 1

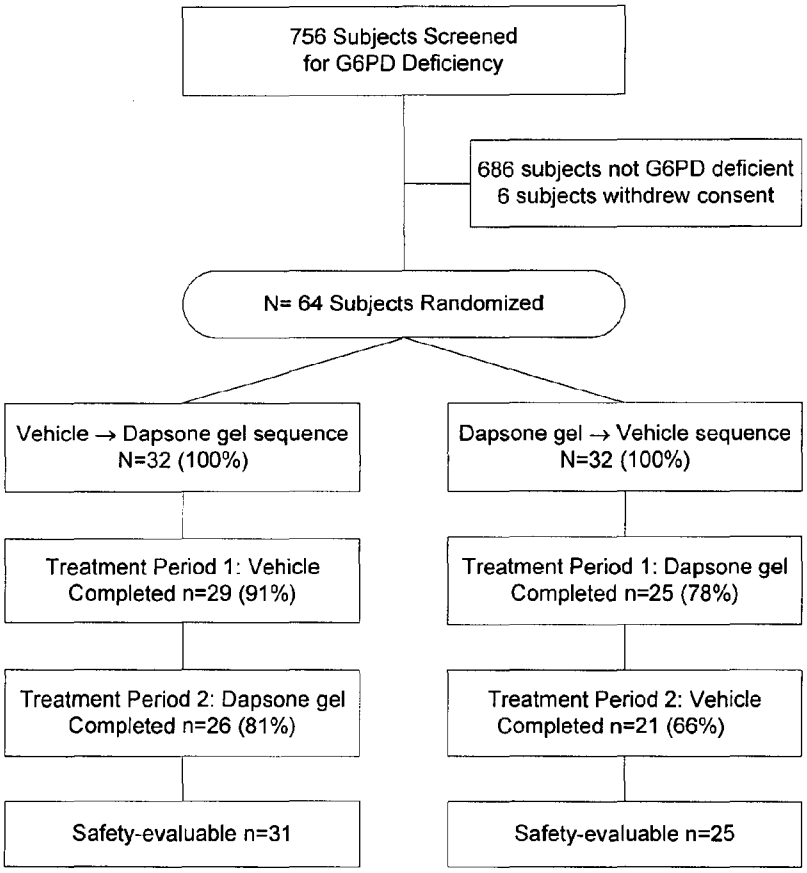

756 Subjects Screened for G6PD Deficiency
686 subjects not G6PD deficient
6 subjects withdrew consent
N= 64 Subjects Randomized
Vehicle → Dapsone gel sequence N=32 (100%)
Dapsone gel → Vehicle sequence N=32 (100%)
Treatment Period 1: Vehicle Completed n=29 (91%)
Treatment Period 1: Dapsone gel Completed n=25 (78%)
Treatment Period 2: Dapsone gel Completed n=26 (81%)
Treatment Period 2: Vehicle Completed n=21 (66%)
Safety-evaluable n=31
Safety-evaluable n=25

Figure 2

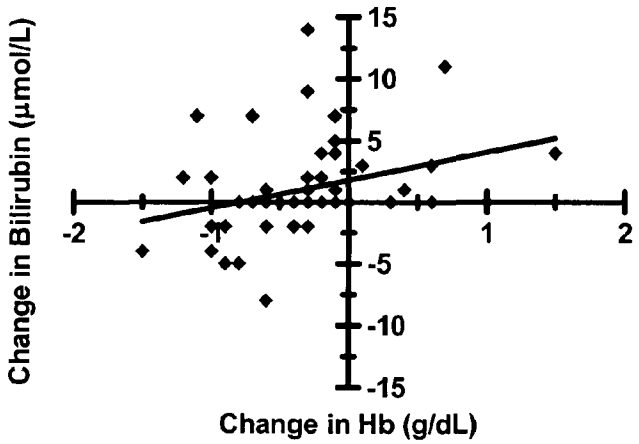


Figure 3

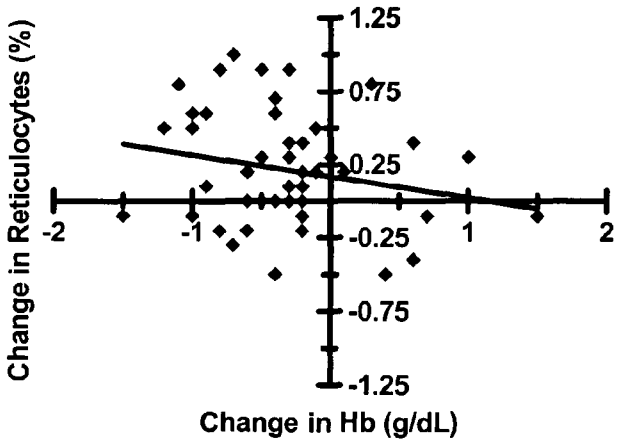

Change in Reticulocytes (%)
1.25
0.75
0.25
-0.25
-0.75
-1.25
-2
-1
1
2
Change in Hb (g/dL)

Figure 4

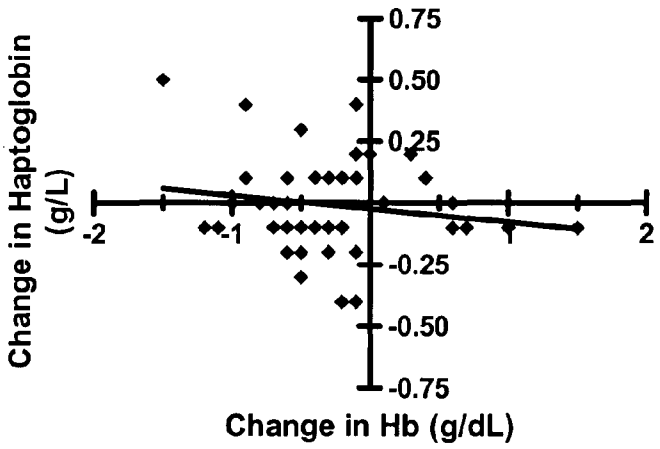
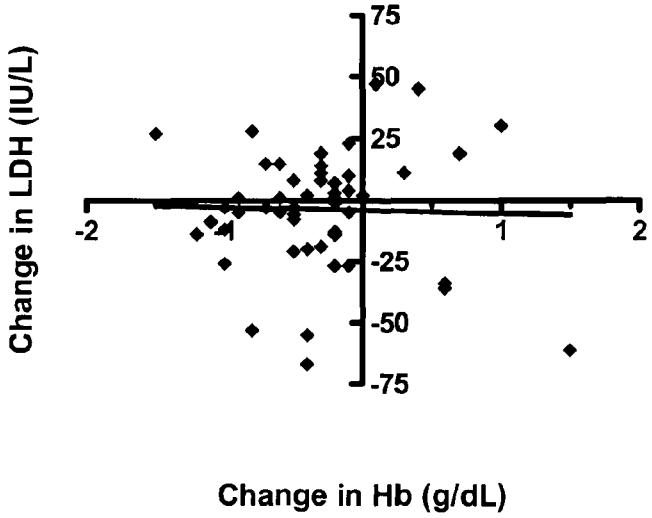

0.75
0.50
0.25
-0.25
-0.50
-0.75
-2
-1
2
Change in Haptoglobin (g/L)
Change in Hb (g/dL)

Figure 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/023468

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/136 A61K9/00 A61K9/06 A61K47/32 A61P17/00
A61P17/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DRAELOS ZOE D ET AL: "Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris." JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY MAR 2007, vol. 56, no. 3, March 2007 (2007-03), pages 439.e1-10, XP002482402 ISSN: 1097-6787 cited in the application page 439.E2, left-hand column, paragraphs 2,3 page 439.E4, left-hand column, last paragraph - right-hand column, paragraph 2; figure 2 page 439.E7, left-hand column, last paragraph - page 439.E8, left-hand column, paragraph 1 ----- -/--	1-27

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2008	13/06/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herdemann, Matthias

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/023468

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANONYMOUS: "ACZONE Gel 55 PACKAGE INSERT"[Online] 2 October 2006 (2006-10-02), XP002482403 Retrieved from the Internet: URL:http://www.fda.gov/cder/foi/label/2005/021794lbl.pdf> [retrieved on 2008-05-30] page 4, lines 1-18 page 5, line 55 - page 6, line 93 page 6, lines 96-105 -----	1-27
X	US 2003/157036 A1 (OSBORNE DAVID W [US]) 21 August 2003 (2003-08-21) abstract paragraph [0013] paragraphs [0021], [0022] paragraph [0028] claim 22; examples 2,3; tables 1,2 -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/023468

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-22 and 24-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/023468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003157036 A1	21-08-2003	AT 353628 T	15-03-2007
		AU 2002306767 A1	09-09-2003
		BR 0215606 A	07-12-2004
		CA 2477217 A1	04-09-2003
		CN 1625384 A	08-06-2005
		DE 60218227 T2	31-10-2007
		DK 1485059 T3	07-05-2007
		EP 1485059 A1	15-12-2004
		ES 2280629 T3	16-09-2007
		IS 7419 A	20-08-2004
		JP 2005524651 T	18-08-2005
		MX PA02006593 A	19-08-2004
		NZ 535363 A	27-04-2007
		WO 03072071 A1	04-09-2003
		ZA 200407439 A	28-06-2002

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(54) Title: DAPSONE TO TREAT ROSASCEA

(57) Abstract: The methods described herein provide treatment of rosacea using topical formulations of dapsone. The methods also provide treatment of rosacea with topical dapsone in combination with other active agents, including metronidazole. The methods avoid negative hematologic side effects, including hemolysis and hemolytic anemia, that are associated with oral administration of dapsone.

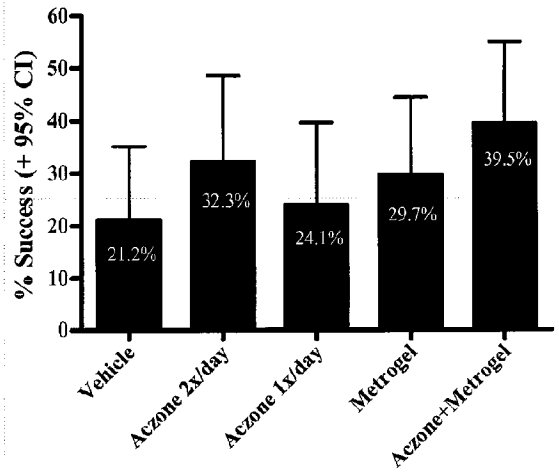

FIG. 11

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DAPSONE TO TREAT ROSACEA

Background of the Invention

Rosacea is a dermatological syndrome affecting approximately 14 million Americans. It is characterized by flushing of the skin, erythema, inflammatory papules and pustules, edema, telangiectasia, ocular symptoms and rhinophyma. To date, the etiology of rosacea is unknown and there is no clearly recognized cure (Bikowski and Goldman, 2004; Stone and Chodosh, 2004).

Four subtypes and one variation of rosacea have been defined. The subtypes are papulopustular rosacea, erythematotelangiectatic rosacea, phymatous rosacea, and ocular rosacea; the rosacea variation is granulomatous rosacea. Some patients may have features of more than one subtype simultaneously, and differences in severity occur within each subtype.

Management of rosacea is difficult because of the complexity of the syndrome and the sensitivity of rosacea-affected skin. Various therapies, including topical application of metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline, are used in the management of rosacea with varying rates of success. Systemic therapy with oral tetracyclines, metronidazole and isotretinoin is also employed in the management of rosacea (Buechner, 2005). Dapsone antibiotic is effective for treating rosacea redness, facial flushing, papules and pustules when administered orally; however, the side effect profile makes the risk/benefit ratio too high for most rosacea sufferers (Nase, 2005).

What is needed are safe, effective treatments for the management of rosacea symptoms.

Summary of the Invention

The invention is directed to the treatment of rosacea. The invention includes a method to treat rosacea by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier to a patient. In preferred embodiments, the rosacea is papulopustular rosacea. In other embodiments, the rosacea is ocular rosacea. The invention is also directed to the

treatment of ocular disorders. The invention includes a method to treat an ocular disease or disorder by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier.

In some embodiments, the dapsone of the topical composition is entirely dissolved in the carrier; or partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid. In an entirely dissolved state, dapsone exists completely in solution in the solvent, with no solid dapsone present. If the dapsone is partially dissolved and partially microparticulate, a portion of the dapsone is present in solution and a portion of the dapsone is present in a solid form. A dapsone emulsion includes two immiscible, unblendable substances wherein one substance (the dispersed phase) is dispersed in the other (continuous phase). The dapsone can be part of the dispersed phase or part of the continuous phase of the emulsion. A dapsone suspension is a heterogenous fluid containing solid particles of dapsone dispersed throughout a fluid. A dapsone colloid is a homogenous mixture of dispersed dapsone particles that are distributed evenly and stably throughout the continuous phase.

In certain embodiments, the pharmaceutical composition is a lotion, gel, ointment, cream, emulsion, suspension, spray, or cleanser. In a preferred embodiment, the pharmaceutical composition is a semisolid aqueous gel. The semisolid aqueous gel includes a thickening agent, water, a solvent, preservative, microparticulate dapsone, dissolved dapsone, and caustic material. In a preferred embodiment, the caustic material is a base agent. In a preferred embodiment, the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum of the epidermis and be absorbed into the lower two-thirds of the pilosebaceous unit; and microparticulate dapsone that is retained in or above the stratum corneum to serve as a reservoir or to provide dapsone to the supracorneum zone, crossing the stratum corneum of the epidermis only minimally as a solid. The solid microparticulate dapsone reservoir is slowly dissolved in body fluids before it is delivered through the stratum corneum. In preferred embodiments, the dapsone makes up about 0.5% to 10% of the pharmaceutical composition. The microparticulate dapsone can be a crystalline precipitate or an amorphous precipitate. Antioxidants, fragrance, colorants, sunscreens, or combinations thereof may also be present in the topical composition. In preferred

embodiments, the dapsone composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

The methods described herein include the treatment of papulopustular rosacea by applying the dapsone composition once or twice daily. In preferred methods the dapsone composition is applied twice daily. The methods additionally include the use of the dapsone pharmaceutical composition alone or in combination with other pharmaceutical compositions for rosacea, including topical and systemic treatments. The treatments are administered simultaneously or sequentially and include oral metronidazole, isotretinoin, tetracyclines including doxycycline, and topical metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline. In some embodiments, the dapsone and other pharmaceutical are present in the same composition. In other embodiments, the dapsone and other pharmaceutical are present in separate compositions. In preferred embodiments, the dapsone pharmaceutical composition is applied topically in the AM and a separate metronidazole composition is applied topically in the PM, or vice versa.

In some embodiments, the patient has mild to severe papulopustular rosacea. In some embodiments, the patient has mild to moderate papulopustular rosacea. In other embodiments, the patient has moderate to severe papulopustular rosacea. In preferred embodiments, the rosacea is moderate to severe papulopustular rosacea. In some embodiments, the patient has at least ten papulopustular lesions before treatment, or preferably at least twenty papulopustular lesions before treatment. In a preferred embodiment, the number of papulopustular rosacea lesions is reduced by administering the dapsone composition topically. In some embodiments, the methods described herein result in blood plasma levels of dapsone of less than about 100 ng/mL.

In some embodiments, the patient has an Investigator's Global Assessment score of 3 or higher before treatment. In some embodiments, treatment results in a mean reduction of at least 13 papulopustular lesions. In some embodiments, treatment results in a mean reduction of at least 43 % of the papulopustular lesions.

Brief Description of the Figures

Figure 1 shows the mean change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line.

Figure 2 shows the mean percent change from baseline in inflammatory lesion counts in the ITT population having ≥ 10 lesions (ITT).

Figure 3 shows mean change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 4 shows mean percent change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 5 shows the mean change from baseline in lesion counts for the subgroup of subjects with ≥ 20 lesions.

Figure 6 shows mean percent change from baseline in inflammatory lesion counts for subjects with ≥ 20 lesions.

Figure 7 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 8 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 9 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with <20 inflammatory lesions.

Figure 10 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with ≥ 20 lesions.

Figure 11 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 for the subgroup of subjects with ≥ 20 lesions.

Detailed Description of the Invention

Definitions

As used herein, "adverse event" means any adverse change in health or "side-effect" that occurs in a patient who is participating in a study while the patient is receiving treatment (dermatological composition or vehicle) or within a pre-specified period of time after their treatment has been completed.

As used herein, the term "colloid" refers to a homogenous mixture of two separate phases. The dispersed phase is made of tiny particles or droplets that are distributed evenly throughout the continuous phase. Colloids are stable mixtures and the dispersed phase generally does not settle out of the mixture.

As used herein, "dapsone" refers to the chemical compound dapsone having the chemical formula $C_{12}H_{12}N_2O_2S$ as well as bis(4-aminophenyl)sulfone, 4',4'-diaminodiphenyl sulfone and its hydrates, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, diaphenylsulfone, dapsone analogs, and dapsone related compounds. "Dapsone analogs" refers to chemical compounds that have similar chemical structures and thus similar therapeutic potential to dapsone such as the substituted bis(4-aminophenyl)-sulfones. "Dapsone related compounds" refers to chemical compounds that have similar therapeutic potential, but are not as closely related by chemical structure to dapsone such as the substituted 2,4-diamino-5-benzylpyrimidines.

As used herein, the term "emulsion" describes a mixture of two immiscible, unblendable substances. The dispersed phase is dispersed in the continuous phase. For example, oil and water will form an emulsion when mixed together. In the compositions described herein, the oil phase may include but is not limited to fatty alcohols, acids, or esters such as cetyl palmitate, cetyl alcohol, stearyl alcohol, stearic acid, isopropyl stearate, glycerol stearate, mineral oil, white petrolatum, or other oils alone or in combination. Surfactants may be present in the emulsion to increase kinetic stability. Suitable emulsifiers that may be added to the compositions described herein include, but are not limited to, steareth 20, ceteth 20, sorbitan sesquioleate, sorbitan mono-oleate, propylene glycol stearate, dosium lauroyl sarcosinate, polysorbate 60, or combinations.

As used herein, "gel" refers to a colloid in a more solid form than a solution. A gel is also a jelly-like material formed by the coagulation of a colloidal liquid. Many gels have a fibrous matrix and fluid filled interstices. Gels are viscoelastic rather than simply viscous and can resist some mechanical stress without deformation.

As used herein, the term "mild rosacea" refers to papulopustular rosacea that includes mild erythema and several small papules/pustules.

As used herein, the term "moderate rosacea" refers to papulopustular rosacea that includes moderate erythema, with several small or large papules/pustules, and up to two nodules.

As used herein, the term "severe rosacea" refers to papulopustular rosacea that includes severe erythema and numerous small and/or large papules/pustules, and up to several nodules.

As used herein, the term "microparticulate" refers to any solid form of an active agent (dapsone) that is not dissolved in the topical composition. The microparticulate described herein may be in the form of flakes or crystals, and includes a precipitate of dapsone that results from the addition of water and the solvent or mixed solvent system. The microparticulate may comprise a crystalline precipitate or an amorphous precipitate.

As used herein, the term "ointment" means a semisolid, oil-based topical formulation. Examples of ointments include essentially non-aqueous mixtures of petrolatum, lanolin, polyethylene glycol, plant or animal oils, either hydrogenated or otherwise chemically modified. An ointment may also contain a solvent in which an active agent is either fully or partially dissolved.

As used herein, "pharmaceutically acceptable carrier" refers to a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering an active agent to a patient. Pharmaceutically acceptable carriers are nontoxic to the cell or patient being exposed thereto at the dosages and concentrations employed. Often, the physiologically acceptable carrier is an aqueous pH buffered solution. Pharmaceutically acceptable carriers are readily available to the public. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Pharmaceutically acceptable carriers may include antiadherents, binders, coatings, disintegrants, fillers, diluents, colorants, glidants, lubricants, and preservatives. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives. In a preferred embodiment, the pharmaceutically acceptable carrier includes ethoxydiglycol, also known as diethylene glycol monoethyl ether (DGME).

As used herein, the term "suspension" refers to a heterogenous fluid containing solid particles dispersed throughout. The suspended phase or suspensoid is dispersed throughout the liquid in a moderately finely divided state, but not so finely divided as to acquire the stability of a colloidal system. The suspended phase will eventually settle out of the suspension.

The term "topical" or "topical surface" as used herein refers to the route of administration of a composition that involves direct application to the surface of the body being treated. Topical application may be to the skin, or to a mucous membrane, also called mucosa, lining all body passages that communicate with the exterior such as the respiratory, genitourinary, and alimentary tracts, and having cells and associated glands that secrete mucous. Topical application may be to mucous membranes of nose, mouth, eye, eyelid inner surface, etc., or may be to the surface of intact or compromised skin. Examples of topical application include application of gels or other semisolids to rub-on, solutions to spray, or liquids to be applied by an applicator, for example, as eye drops. Rinse-off application with washes, cleansers, or shampoos are also examples of topical application. Areas of the body especially suitable for application of the composition described herein include sites where rosacea symptoms may be present, including the skin of the face, scalp, ears and neck, and the eyes.

As used herein, the term "treat", "treatment", or "treating" refers to the reduction in number and/or severity of individual rosacea lesions, prevention of the development of rosacea symptoms including papulopustular lesions, or global improvement in the appearance of rosacea. Success of treatment may be indicated by a reduction from baseline in the raw number of papulopustular inflammatory lesions, by a percent reduction from baseline in papulopustular inflammatory lesions, or by an improvement from baseline in an Investigator's Global Assessment (IGA) score.

Methods of Treatment

The method of the invention described herein treats rosacea conditions, e.g., papulopustular, erythematotelangiectatic, phymatous, and ocular rosacea, by the topical application of a composition comprising dapsone and a pharmaceutically acceptable carrier. The composition is applied as needed to relieve rosacea symptoms. In some embodiments, the composition is applied

every other day. In some embodiments, the composition is applied once daily. In some embodiments, the composition is applied twice daily. In certain embodiments, the composition is applied for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, at least eight weeks, at least nine weeks, at least ten weeks, at least eleven weeks, or at least twelve weeks. In some preferred embodiments, the composition is applied for at least twelve weeks. In other preferred embodiments, the composition is applied for at least six months, at least nine months, or at least a year.

Rosacea

Rosacea is a multifactorial chronic disorder that most often affects the skin of the central face including the nose, forehead, cheeks, and chin. Rosacea usually affects fair-skinned people 30 to 50 years of age who tend to blush or flush easily. Four subtypes of rosacea are described: papulopustular, erythematotelangiectatic, phymatous, and ocular (Wilkin et al. 2002; Bikowski and Goldman, 2004). Granulomatous rosacea is considered to be a part of the spectrum of rosacea, but is referred to as a variant, rather than a subtype, of rosacea (Khokhar and Khachemoune 2004).

Papulopustular rosacea is characterized by persistent central facial erythema with transient, central facial papules, pustules or lesions of both types. In preferred embodiments, mild to severe papulopustular rosacea is treated. In a more preferred embodiment, moderate to severe papulopustular rosacea is treated. Erythematotelangiectatic rosacea is characterized by flushing and persistent central facial erythema, with or without telangiectasia. Phymatous rosacea is characterized by thickening skin, irregular surface nodularities, and enlargement, which may occur on the nose, chin, forehead, cheeks or ears. Ocular rosacea is characterized by a foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema. Granulomatous rosacea is characterized by noninflammatory, hard, brown, yellow or red cutaneous papules; or nodules of uniform size (Bikowski and Goldman, 2004).

In a recent study of clinical patterns of rosacea, papules and pustules were found in 83% and 67% of a sample of 108 rosacea patients, respectively

(Sibenge and Gawkrodger, 1992). In the papulopustular subtype of rosacea, patients typically present with persistent central facial erythema with transient papules or pustules or both. Symptoms of burning, stinging, and dry skin are common (Wilkin et al. 2002; Dahl 2004). Other symptoms include flushing, erythema, and telangiectasia. While the exact pathogenesis of rosacea is unknown, inflammatory and vascular components are believed to be important in its pathogenesis.

The methods of the invention described herein include treatment of papulopustular rosacea lesions. In certain embodiments, the treatment of rosacea lesions results in a decrease or reduction from the baseline number of lesions by at least 2 lesions, at least 3 lesions, at least 4 lesions, at least 5 lesions, at least 6 lesions, at least 7 lesions, at least 8 lesions, at least 9 lesions, at least 10 lesions, at least 11 lesions, at least 12 lesions, at least 13 lesions, at least 14 lesions, at least 15 lesions, at least 16 lesions, at least 17 lesions, at least 18 lesions, at least 19 lesions, at least 20 lesions, at least 30 lesions, at least 40 lesions, or more than 40 lesions. In certain embodiments, the treatment of rosacea lesions results in a percentage decrease or reduction of lesions from baseline of at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, or more than 75%.

About half of all rosacea sufferers also have some involvement of the eyes, known as ocular rosacea (Starr and McDonald, 1969). Eye problems may precede the common skin-related rosacea symptoms though it more common for the skin symptoms to appear first (Borrie, 1953). Ocular rosacea symptoms include dry eyes or tearing, redness, burning, pain, a gritty feeling in the eye, scales and crusts on the eyelids, sensitivity to light and blurry vision (Jenkins 1979).

Blepharitis, which includes inflammation of eyelashes or lid margins, is commonly seen in ocular rosacea. Blepharitis often results in red, itchy, burning eyes and lashes as well as scales and crusts on the eyelids. Sties, which are infections of eyelash follicles, may be present. Ocular rosacea sufferers may also have chalazia or meibomitis, characterized by enlarged, inflamed or plugged meibomian glands (which normally lubricate the eyelids). Scleritis and episcleritis, which are inflammatory conditions of the white outer coating of the

eye (sclera) and connective tissue between the conjunctiva and sclera (episclera) may also be present in ocular rosacea.

Keratitis and iritis, which are infections or inflammation of the cornea and iris, respectively, may also be present in patients with ocular rosacea. These conditions may result in severe eye pain, blurry vision, formation of pus, and sensitivity to light. In severe ocular rosacea, ulcers may be present at the border of the cornea and sclera. This corneal ulceration, if untreated, may lead to perforation of the eye, a potentially blinding complication.

Management of rosacea is difficult because of the complexity of the syndrome and the sensitivity of rosacea-affected skin. Various therapies, including topical application of metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline, are used in the management of rosacea with varying rates of success. Systemic therapy with oral tetracyclines, metronidazole and isotretinoin is also employed in the management of rosacea (Buechner, 2005). Oral dapsone antibiotic is effective for treating rosacea redness, facial flushing, papules and pustules; however, the side effect profile makes the risk/benefit ratio too high for most rosacea sufferers (Nase, 2005).

Ocular Indications

In addition to ocular rosacea, other ocular diseases may be treated with the topical dapsone compositions of the present invention. These diseases may be associated with inflammation, infection or other pathologies and the ocular involvement may be a primary or secondary manifestation of the disease or disorder. These diseases and disorders include conjunctivitis; scleritis including nodular scleritis secondary to Sweet's syndrome; vasculitis including autoimmune vasculitis and retinal vasculitis of Eales' disease; uveitis including granulomatous uveitis and panuveitis; ocular cicatrical pemphigoid; ocular leprosy; ocular manifestations of arachnid evenomation, Behçet disease, linear IgA disease, relapsing polychondritis, peripheral keratitis, tuberculosis, Hodgkin lymphoma, non-Hodgkin lymphoma, T-cell lymphoma and Reiter's syndrome; tumors of the eyelids; erythema elevatum diutinum; eyelid manifestations of erosive lichen planus; and pneumocystis carinii choroiditis associated with AIDS. The topical dapsone compositions of the present invention may be particularly formulated for treatment of ocular conditions. These formulations

will be known to those of skill in the art and include drops, gels, ointments, cleansers and other topical formulations.

Dapsone

Dapsone was first synthesized in 1908 and has been used medically as an antibiotic and an anti-inflammatory. Dapsone is a bis(4-aminophenyl)sulfone also known as 4',4'-diaminodiphenyl sulfone, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, and diaphenylsulfone. Dapsone has been used orally for the treatment of acne (Ross, 1961).

Dapsone analogs and related compounds have been described in U.S. Pat. Nos. 4,829,058 and 4,912,112 to Seydel et al. The '058 patent discloses substituted bis(4-aminophenyl)sulfones useful for inhibiting growth of bacteria, mycobacteria, and plasmodia. Some of these compounds were also tested against dapsone for toxicity and anti-inflammatory activity. In the '112 patent, substituted 2,4-diamino-5-benzyl pyrimidines having antimicrobial activity particularly against mycobacteria are described. Some of these compounds were also tested against dapsone for toxicity (Coleman et al., 1996) and anti-inflammatory activity (Coleman et al., 1997). The teachings of these references in combination with subsequent publications showed that these analogs and related compounds have activity similar to dapsone and would be expected to have similar treatment efficacy.

Currently, use of oral dapsone is generally limited, as its use may be associated with hematologic side effects, including hemolysis and hemolytic anemia that are dose-dependent and occur more frequently with increasing dose (Zhu and Stiller 2001; Jollow et al., 1995). The mechanism of dapsone-related hemolysis and hemolytic anemia involves oxidative damage to red blood cells and is associated with the dapsone hydroxylamine metabolite (Prendiville et al., 1988).

Topical Dapsone Compositions

Topical dapsone formulations have been described in U.S. Pat. No. 5,733,572 to Unger et al., and U.S. Pat. Nos. 6,056,954; 6,056,955; 6,254,866; 6,248,324; and 6,277,399 to Fischetti et al. A topical composition including dapsone for acne treatment has been described in U.S. Pat. Nos. 5,863,560 and 6,060,085 to Osborne which are herein incorporated by reference in their entirety.

The topical compositions described herein include dapsone and a pharmaceutically acceptable carrier. The carriers described herein are media useful for topical delivery of dapsone and optionally any additional active agents. These media, which are preferably organic or organic/aqueous mixtures, may be formulated as eye drops, lotions, gels, ointments, creams, sprays, washes, cleansers, shampoos, roll-on or stick products, micro-emulsions, shake powders, aerosolized sprays or mousse, and bath additives. Additional pharmaceutical carriers will be known to those skilled in the art and this list should not be considered to be limiting.

The dapsone of the topical composition may be entirely dissolved in the carrier; partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid. In an entirely dissolved state, dapsone exists completely in solution in the solvent, with no solid dapsone present. If the dapsone is partially dissolved and partially microparticulate, a portion of the dapsone is present in solution and a portion of the dapsone is present in a solid form. A dapsone emulsion includes two immiscible, unblendable substances wherein one substance (the dispersed phase) is dispersed in the other (continuous phase). The dapsone can be part of the dispersed phase or part of the continuous phase of the emulsion. A dapsone suspension is a heterogenous fluid containing solid particles of dapsone dispersed throughout a fluid. A dapsone colloid is a homogenous mixture of dispersed dapsone particles that are distributed evenly and stably throughout the continuous phase.

Pharmaceutical carriers are pharmaceutically acceptable media for delivering active agent(s) to a patient. Pharmaceutically acceptable carriers include solvents, suspending agents or other vehicles that are nontoxic to the patient being exposed thereto at the dosages and concentrations employed. Pharmaceutical carriers of the compositions described herein will solubilize dapsone and any additional active agent(s) in whole or in part. Excipients present in the pharmaceutically acceptable carrier may include antiadherents, binders, coatings, disintegrants, fillers, diluents, colorants, glidants, lubricants, and preservatives.

In some embodiments, the topical compositions include a pharmaceutical carrier, dapsone, and an additional active pharmaceutical agent or agents. As described above, these dual agent compositions may be formulated as lotions,

gels, ointments, creams, sprays, washes, cleansers, shampoos, roll-on or stick products, micro-emulsions, shake powders, aerosolized sprays or mousse, and bath additives. The dapsone and additional active pharmaceutical agent(s) of the topical composition may be entirely dissolved; partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid as described above. Suitable additional active pharmaceutical agents are disclosed, e.g., in Physician's Desk Reference (PDR), Medical Economics Company (Montvale, NJ), (53rd Ed.), 1999; Mayo Medical Center Formulary, Unabridged Version, Mayo Clinic (Rochester, MN), January 1998; Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, (11th Ed.), Merck & Co., Inc. (Rahway, NJ), 1989; and references cited therein.

Additional active pharmaceutical agents include, but are not limited to, anti-inflammatory agents, keratolytics, anti-infectives and acidic compounds. Anti-inflammatory agents, including corticosteroids, relieve inflammation including swelling, itching, and redness of the skin. Keratolytics are agents that soften skin cells and ease the flaking and peeling process. Examples include salicylic acid and urea. Anti-infectives including antibiotics, antifungals and antiseptics combat bacteria, fungi, and parasites. Acidic compounds contain an organic acid group or are at least weakly acidic in an aqueous-based solution and include retinoic acid, azelaic acid and lactic acid. In preferred embodiments, the additional active pharmaceutical agent is metronidazole anti-infective.

In preferred embodiments, the topical compositions described herein include thickening agents or thickeners. These substances increase viscosity, stability and improve suspending capability when added to a mixture. Known thickeners include inorganic water thickeners, polymeric thickeners, additives that promote thickening via lamellar structuring of surfactants, organic crystalline thickeners, and mixtures thereof. Suitable polymer thickeners for use in the topical compositions include cationic thickeners, non-ionic thickeners and anionic thickeners. Useful thickeners are described in detail below.

In preferred embodiments, the topical compositions described herein include solvent systems comprising organic solvents. These carbon-containing liquids dissolve solids, liquids, or gaseous solutes to form a solution. Solvents are grouped into polar (hydrophilic) and non-polar (lipophilic) types. Useful solvents are described in detail below. In preferred embodiments, the solvent of

the topical compositions is diethylene glycol monoethyl ether (DGME), also known as ethoxydiglycol. In preferred embodiments, the topical composition of dapsone is formulated as an eye-drop and the solvent of such eye-drop compositions comprises a non-irritating solvent, more preferably diethylene glycol monoethyl ether (DGME), even more preferably DGME sold under the trade name "Transcutol™", even more preferably DGME having a percent purity of greater than 99.5%, such as those sold under the name "Transcutol™ CG," "Transcutol™ P" and "Transcutol™ HP."

Preservatives, antioxidants, fragrances, colorants, sunscreens, thickeners, suspending agents, enhancers, binders, disintegrants, fillers, diluents, colorants, glidants, lubricants, and other additives required to achieve pharmaceutically or cosmetically acceptable properties of the topical compositions may also be included. Topical compositions are not limited to these components, since one skilled in the art will be aware of additional components useful in the formulation of topical compositions.

The present compositions can include an alkali, also known as a base agent or caustic agent. The amount of alkali can be adjusted to change pH values of the topical compositions. The pH adjustment of the compositions of the present invention can be carried out by means of inorganic bases such as sodium hydroxide and potassium hydroxide; and organic bases such as triethylamine, diisopropanolamine, and triethanolamine (trolamine). The compositions may have a pH of about 7, e.g. 7.2, or below about 7. In other embodiments, the compositions of the present invention can be adjusted to have a pH below about 6.0, more specifically below about 5.5, even more specifically between about 4.0 to about 5.5, even more specifically between about 4.2 to about 5.4, or 4.4 to about 5.2, or about 4.8 ± 0.5.

Thickeners

Suitable thickeners for use in the topical compositions include non-ionic thickeners, cationic thickeners and anionic thickeners. Suitable non-ionic thickening agents include polyacrylamide polymers, crosslinked poly(N-vinylpyrrolidones), polysaccharides, natural or synthetic gums, polyvinylpyrrolidone and polyvinylalcohol. Specific examples of non-ionic thickening agents include methyl hydroxypropyl cellulose, xanthan gum, polysaccharide gum, hydroxyl propyl cellulose, hydroxyl propyl methyl

cellulose, hydroxyl ethyl cellulose, polyalkylene gylcols, and mixtures thereof. Suitable anionic thickening agents include acrylic acid/ethyl acrylate copolymers, carboxyvinyl polymers and crosslinked copolymers of alkyl vinyl ethers and maleic anhydride.

Polymer thickeners that may be used include those known to one skilled in the art, such as hydrophilic and hydroalcoholic gelling agents frequently used in the cosmetic and pharmaceutical industries. Preferably, the hydrophilic or hydroalcoholic gelling agent comprises "CARBOPOL®" (B.F. Goodrich, Cleveland, Ohio), "HYPAN®" (Kingston Technologies, Dayton, N.J.), "NATROSOL®" (Aqualon, Wilmington, Del.), "KLUCEL®" (Aqualon, Wilmington, Del.), or "STABILEZE®" (ISP Technologies, Wayne, N.J.). Preferably, the gelling agent comprises between about 0.2% to about 4% by weight of the composition. More particularly, the preferred compositional weight percent range for "CARBOPOL®" is between about 0.5% to about 2%, while the preferred weight percent range for "NATROSOL®" and "KLUCEL®" is between about 0.5% to about 4%. The preferred compositional weight percent range for both "HYPAN®" and "STABILEZE®" is between about 0.5% to about 4%.

"CARBOPOL®" is one of numerous cross-linked acrylic acid polymers that are given the general adopted name carbomer. These polymers dissolve in water and form a clear or slightly hazy gel upon neutralization with a caustic material such as sodium hydroxide, potassium hydroxide, triethanolamine, or other amine bases. "KLUCEL®" is a cellulose polymer that is dispersed in water and forms a uniform gel upon complete hydration. Other preferred gelling polymers include hydroxyethylcellulose, cellulose gum, MVE/MA decadiene crosspolymer, PVM/MA copolymer, or a combination thereof.

Solvents

In some embodiments, the topical compositions described herein are fluid solvent or mixed-solvent systems. The solvent can be an organic solvent, for example the solvent can include diethyleneglycol monoethyl ether (DGME), N-methylpyrrolidone (NMP), N,N-dimethylformamide, N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or any other substantially non-toxic solvent suitable for application to human skin, wherein the solvent has at least some water solubility. Combinations of any of these solvents can also be used. Additional examples of solvents include ethanol, propylene glycol, glycerol,

diethyleneglycol, triethyleneglycol, polyethylene glycol, propylene carbonate, pyrrolidone, *N*-methyl pyrrolidone, dimethylsulfoxide, triethanolamine, 1,4-butanediol, ethyl acetate, triacetin, diacetin, dimethyl isosorbide, and the like, alone or in combination.

Other solvents can be used in conjunction with water to form the liquid of the inventive method. These solvents include, but are not limited to: benzyl alcohol, denatured alcohol, methanol, isopropyl alcohol, propanol, acetone, chlorobutanol, methyl ethyl ketone, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, butyl alcohol, diglycerides, dipropylene glycol, eugenol, diacetin, diethanolamine, monoacetin, monoglycerides, PEG vegetable oil, N,N-dimethylformamide, N-methyl formamide, N-methylacetamide, N,N-dimethylacetamide, or combinations thereof.

Glycol ethers are organic solvents that are moderately soluble to miscible with water and can be used as a solvent in formation of a composition used in the methods described herein. A glycol ether is an ether formed from at least one glycol and at least one lower alkyl alcohol. Preferably the glycol is selected from an alkylene glycol such as ethylene glycol, propylene glycol, and butylene glycol. The ether portion of the glycol ether is a radical of a lower alkyl alcohol such as a C_1 to C_6 alcohol. Preferably, the ether portion alcohol is selected from methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, and isobutyl alcohol.

Examples of glycol ethers under the classification of ethylene glycol ethers include ethylene glycol monopropyl ether (propoxyethanol), ethylene glycol monobutyl ether (butoxyethanol), diethylene glycol monoethyl ether (ethoxydiglycol, DGME), diethylene glycol monobutyl ether (butoxydiglycol), diethylene glycol monoisopropyl ether (isopropyldiglycol), and diethylene glycol monoisobutyl ether (isobutyl diglycol).

Glycol ethers under the classification of propylene glycol ethers include propylene glycol monomethyl ether, dipropylene glycol monomethyl ether (PPG-2 methyl ether), tripropylene glycol monomethyl ether (PPG-3 methyl ether), propylene glycol n-propyl ether, dipropylene glycol n-propyl ether (PPG-2 propyl ether), propylene glycol monobutyl ether, dipropylene glycol monobutyl ether (PPG-2 butyl ether), propylene glycol monoisobutyl ether, and dipropylene glycol dimethyl ether. In one embodiment of the invention the

solvent is ethoxydiglycol. Additional suitable exemplary glycol ethers are disclosed, e.g., in Aldrich Handbook of Fine Chemicals, 2003-2004 (Milwaukee, WI).

In some embodiments, compositions of the invention have a glycol ether present in about 20 wt.% to about 40.0 wt.%. In some embodiments, compositions of the invention have a glycol ether present in about 20.0 wt.% to about 35.0 wt.%. In some embodiments, compositions of the invention have a glycol ether present in about 25.0 wt.% to about 40.0 wt.%. In yet another embodiment, compositions of the present invention have a glycol ether present in about 25.0 wt.% to about 35.0 wt.% of the composition. More specifically, compositions of the present invention have a glycol ether present in about 25.0 wt.% of the composition.

Additives

Preservatives may also be used in the pharmaceutical composition and preferably comprise about 0.05% to 0.5% by weight of the total composition. The use of preservatives assures that if the product is microbially contaminated, the formulation will prevent or diminish microorganism growth. Some preservatives useful in the pharmaceutical composition include methylparaben, propylparaben, butylparaben, chloroxylenol, sodium benzoate, DMDM Hydantoin, 3-Iodo-2-Propylbutyl carbamate, potassium sorbate, chlorhexidine digluconate, or a combination thereof.

Titanium dioxide may be used as a sunscreen to serve as prophylaxis against photosensitization. Alternative sunscreens include methyl cinnamate. Moreover, BHA may be used as an antioxidant, as well as to protect ethoxydiglycol and/or dapsone from discoloration due to oxidation. An alternate antioxidant is BHT.

Preferred formulations

As described herein, rosacea is treated by topically applying a topical composition comprising dapsone. In some embodiments, the topical composition comprises dissolved dapsone. In preferred embodiments, the topical composition is a pharmaceutical carrier system that is an aqueous gel, wherein the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum to become systemically available, and microparticulate dapsone that is retained above the stratum

corneum to serve as a reservoir or to provide dapsone to the supracorneum zone, crossing the stratum corneum of the epidermis only minimally as a solid. The solid microparticulate dapsone reservoir is slowly dissolved in body fluids and then delivered through the stratum corneum. In some embodiments, the microparticulate dapsone is any solid form of dapsone that is added to a saturated solution of dapsone. In other embodiments, the microparticulate dapsone may be a precipitate formed by the addition of water to a solution containing a solvent and dapsone. The precipitate may comprise a crystalline precipitate or an amorphous precipitate.

Optimal balance is accomplished by having a gel carrier system in which microparticulate dapsone is formed in reproducible ratios with respect to the dissolved dapsone. For the composition to have a wide range of applicability, the microparticulate to dissolved dapsone ratio preferably should be no greater than five, at therapeutic levels of applied active dapsone.

A composition having a microparticulate to dissolved dapsone ratio of less than two may provide the greatest amount of pharmaceutical available for immediate partition out of the stratum corneum and into the viable epidermis. This should provide minimum reservoir capacity, and may not maintain sustained delivery or provide maximum activity in the supracorneum zone. A composition having a microparticulate to dissolved dapsone ratio of two or greater may have a reduced amount of drug available for immediate partition out of the stratum corneum and into the viable epidermis. This provides maximum reservoir capacity, maintains sustained delivery through the stratum corneum by slowly dissolving the dapsone in body fluids, and provides activity in the supracorneum zone. For the present invention, the ratio for microparticulate drug to dissolved drug should be no greater than 50, and preferably no greater than 10. More preferably, the ratio for microparticulate drug to dissolved drug should be no greater than 7 or no greater than 6. Most preferably, the ratio for microparticulate drug to dissolved drug should be about 5.5, 5.4, 5.3, 5.2, 5.1 or 5.0. In some embodiments, the ratio for microparticulate drug to dissolved drug should be no greater than 5. Drug delivery from the microparticulate/dissolved dapsone formulation may be optimized to provide higher levels of drug to the supracorneum zone, while maintaining the level of drug partitioning through the

stratum corneum and into the viable epidermis, despite 10-fold increases in the amount of pharmaceutical applied to the topical surface.

The compositions of the present invention comprise semi-solid and gel-like vehicles that include a thickener, water, preservatives, active surfactants or emulsifiers, antioxidants, sunscreens, and a solvent or mixed solvent system. The solvent or mixed solvent system is important to the formation of the microparticulate to dissolved dapsone ratio. The formation of the microparticulate, however, should not interfere with the ability of the thickener or preservative systems to perform their functions.

In a preferred embodiment, the topical composition comprises a thickening agent; water; a high-boiling, nonionic organic solvent; a preservative; dapsone in a microparticulate and dissolved state; and a base solution. In one embodiment, the topical composition that is applied includes about 0.5% to 4.0% carbomer and about 0.5% to 10% of dapsone that exists in both a dissolved state and a microparticulate state. The dissolved dapsone has the capacity to cross the stratum corneum, whereas the microparticulate dapsone does not. Addition of an amine base, potassium hydroxide solution, or sodium hydroxide solution completes the formation of the gel. A preferred ratio of microparticulate to dissolved dapsone is approximately five, which includes 5.5, 5.4, 5.3, 5.2, 5.1 and 5.0.

In some embodiments, the topical composition comprises about 5% dapsone, about 4% dapsone, about 3% dapsone, about 2% dapsone, or about 1% dapsone. In other embodiments, the topical composition comprises between 0.5% and 5% dapsone. In still other embodiments, the topical composition comprises between 0.5% and 10% of dapsone. In another embodiment, the pharmaceutical composition comprises about 1% carbomer, about 80-90% water, about 10% ethoxydiglycol (DGME), about 0.2% methylparaben, about 0.3% to 3.0% dapsone including both microparticulate dapsone and dissolved dapsone, and about 2% caustic material. More particularly, the carbomer may include "CARBOPOL® 980" and the caustic material may include sodium hydroxide solution.

In another embodiment, the composition comprises dapsone and ethoxydiglycol (DGME), which allows for an optimized ratio of microparticulate drug to dissolved drug. This ratio determines the amount of drug delivered,

compared to the amount of drug retained above the stratum corneum to function as a reservoir or for action in the supracorneum domain. The system of dapsone and ethoxydiglycol may include purified water combined with "CARBOPOL®" gelling polymer, methylparaben, propylparaben, titanium dioxide, BHA, and a caustic material to neutralize the "CARBOPOL®."

In a preferred embodiment, the composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide; and about 68.75% purified water.

The relative percentages for each of the reagents used in the pharmaceutical composition may vary depending upon the desired strength of the target formulation, gel viscosity, and the desired ratio of microparticulate to dissolved dapsone. Unless otherwise designated, all reagents listed above are commonly known by one of ordinary skill in the art and are commercially available from pharmaceutical or cosmetic excipient suppliers.

Additional agents for combination therapy

It is contemplated that the methods described herein may include the use of other topical formulations in combination with topical dapsone. There are a number of specific courses of treatment that can be carried out. In some embodiments, the dapsone topical formulation and other topical formulation are administered simultaneously. In other embodiments, the dapsone topical formulation and other topical formulation are administered sequentially. Over the course of treatment, the administration of one formulation can continue when the other is discontinued and vice versa.

It is further contemplated that the methods described herein may include the use of other active pharmaceutical ingredients in combination with dapsone in a single topical composition. In these embodiments, the dapsone and other active ingredient are administered simultaneously.

Other topical formulations and active agents contemplated to be employed in conjunction with topical dapsone include, but are not limited to, metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline. In one combination regimen, dapsone is applied in the AM and metronidazole is

applied in the PM. In another combination regimen, metronidazole is applied in the AM and dapsone is applied in the PM.

It is further contemplated that the methods described herein include the use of systemic rosacea therapy in combination with topical dapsone therapy. Contemplated systemic therapies for use in combination with topical dapsone therapy include, but are not limited to, oral metronidazole and isotretinoin, and tetracyclines including doxycycline.

In one specific embodiment of the invention, the dapsone composition can be co-administered with photochemotherapy with ultraviolet A (PUVA). In another specific embodiment of the invention, the dapsone compositioncan be co-administered with phototherapy with UVB. As used herein, "photochemotherapy with ultraviolet A (PUVA)" refers to a type of ultraviolet radiation treatment (phototherapy) used for severe skin diseases. PUVA is a combination treatment which consists of Psoralen (P) administration and then exposure of the skin to long wave ultraviolet radiation (UVA).

Dapsone plasma levels

An advantage of the methods described herein is that blood plasma levels of dapsone and metabolites including N-acetyl dapsone and N-hydroxylamine dapsone are greatly reduced in comparison to oral administration of dapsone. The methods described herein employing topical dapsone are contemplated to result in blood plasma levels of dapsone and metabolites including N-acetyl dapsone and N-hydroxylamine dapsone less than about 150 ng/mL, less than about 100 ng/mL, less than about 90 ng/mL, less than about 80 ng/mL, less than about 70 ng/mL, less than about 60 ng/mL, less than about 50 ng/mL, less than about 40 ng/mL, less than about 30 ng/mL, less than about 20 ng/mL, less than about 10 ng/mL, less than about 9 ng/mL, less than about 8 ng/mL, less than about 7 ng/mL, less than about 6 ng/mL, less than about 5 ng/mL, less than about 4 ng/mL, less than about 3 ng/mL, less than about 2 ng/mL, and less than about 1 ng/mL.

Methods for Preparing Dapsone Topical Compositions

Those skilled in the art will be familiar with formulation methods used in preparing topical solutions or suspensions, lotions, ointments, creams and other formulations described above.

In some embodiments of the invention, a composition having dissolved dapsone and microparticulate dapsone is generally prepared by completely dissolving dapsone in a solvent or solvent mixture; adding and adequately dispersing a polymeric thickener in water; and combining the dissolved dapsone with the dispersed polymeric thickener. Alternatively, water may be slowly added to the dissolved dapsone, followed by the addition of a polymeric thickener. Ethoxydigylcol (DGME) and 1-methyl-2-pyrollidone are preferred solvents for use in the topically applied composition.

In some embodiments of the invention, the composition having dissolved dapsone and microparticulate dapsone is prepared by first forming a liquid by combining an organic solvent and water, and then contacting dapsone in a microparticulate solid form with the liquid, such that the microparticulate solid dapsone form does not entirely dissolve in the liquid; and dissolving a thickener in the liquid at a concentration sufficient to form a gel. In another embodiment of the invention, the composition having dissolved dapsone and microparticulate dapsone is prepared by, prior to the step of contacting the microparticulate solid dapsone with the liquid, forming a solution of the dapsone in the liquid, wherein the dapsone is substantially completely dissolved in the liquid.

In a preferred embodiment, the method for preparing a topically applied composition having dissolved and microparticulate dapsone comprises the steps of forming a homogenous dispersion by stirring purified water vigorously enough to form a vortex and sifting gel polymer into the vortex formed in the water while continuing to stir; forming a pharmaceutical component by dissolving methyl paraben and/or propylparaben in ethoxydiglycol by mixing to form a solution, and mixing dapsone with the solution until the pharmaceutical is dissolved; mixing the pharmaceutical component with the homogenous dispersion to form a microparticulate dapsone dispersion; and adding a caustic material.

The order in which reagents are combined may be important, depending on the particular reagents necessary for the target mixture. For example, after a pharmaceutical such as dapsone is dissolved in a solvent such as ethoxydiglycol, water may be slowly added to the dapsone in the ethoxydiglycol solution, or the dapsone in ethoxydiglycol solution may be added to the water with mixing. Adding the dapsone in ethoxydiglycol solution to water may result in less

polydispersity in the size of the microparticulates than adding water to the dapsone in ethoxydiglycol solutions. The carbomer is generally dispersed in the water component of the formulation, while the remaining ingredients will be dissolved or dispersed in whichever of the two components are best for dissolving or dispersing the ingredient. For example, it is suggested to dissolve methylparaben, propylparaben, and BHA in ethoxydiglycol. After the ethoxydiglycol component and water component are combined, neutralizer is added to formulate the gel.

As described below, a study was conducted using as test subjects 399 male and female subjects $\geq$ 18 years of age. At baseline, the subjects had a diagnosis of papulopustular rosacea, with $\geq$ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. There was an overall improvement from baseline in local symptom scores with treatment. While treatment showed efficacy for patients with $\geq$ 10 inflammatory lesions, improved results were shown for subjects who entered the study with $\geq$ 20 inflammatory papulopustular lesions. It was surprising that the treatment was more successful for a more severe form of the disease. Topical application of 5% dapsone is safe and well tolerated when used to treat subjects with papulopustular rosacea. Systemic levels of dapsone and its metabolites were low during the study with no evidence of increasing exposure over time. No subjects in the study demonstrated evidence of hemolysis or treatment related hematological adverse events.

The invention will be described by the following non-limiting example.

Example 1

Methods

A twelve week study was conducted in 399 male and female subjects $\geq$ 18 years of age. At baseline, the subjects had a diagnosis of papulopustular rosacea, with $\geq$ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. Each subject had an Investigator Global Assessment (IGA) score $\geq$ 2, as defined in Table 1.

Table 1: Investigator Global Assessment of Disease Severity

Score	Severity	Description
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

The subjects were randomly assigned to one of the following five treatment groups:

1) Vehicle Control (VC), 2x/day (80 subjects).
2) Aczone™ Gel, 5%, 2x/day (84 subjects).
3) Aczone™ Gel, 5%, 1x/day (79 subjects).
4) MetroGel® (metronidazole gel), 1%, 1x/day (80 subjects).
5) Aczone™ Gel, 5% 1x/day + MetroGel® (metronidazole gel), 1%, 1x/day (76 subjects).

MetroGel® is a 1% gel formulation of metronidazole. Metronidazole has been used as a topical therapy for rosacea since its approval in 1988 and is effective in reducing inflammatory papules and pustules and producing overall improvement in rosacea symptoms (Bikowski and Goldman, 2004).

MetroGel® contained the active ingredient metronidazole (10 mg per gram). Inactive ingredients in MetroGel® included: betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide, phenoxyethanol, propylene glycol, propylparaben, and purified water.

Aczone™ Gel is a 5% gel formulation of dapsone. Aczone™ gel contained the active ingredient dapsone (50 mg per gram). Inactive ingredients in the Aczone™ gel included: carbomer 980, diethylene glycol monoethyl ether (DGME), methylparaben, sodium hydroxide, and purified water. The vehicle control (VC) contained only the inactive components carbomer 980, diethylene glycol monoethyl ether (DGME), methylparaben, propylparaben, sodium hydroxide, and purified water.

The Aczone™ (dapsone 5%) gel was prepared as follows:

A polymer thickener component was prepared by charging 66.95 grams of purified water to a vessel suitable to contain 100 grams of finished semisolid

product, and 0.85 g of "CARBOPOL® 980" was slowly sifted into a vortex formed by rapidly stirring the purified water. When a homogeneous dispersion of "CARBOPOL® 980" and water was formed, stirring was reduced to minimize air entrapment. Next, an active pharmaceutical component was prepared by charging an appropriately sized container with 25 g of ethoxydiglycol, then 0.2 g of methylparaben were added to the ethoxydiglycol and mixed until all of the crystalline solid was dissolved. 5.0 g dapsone was added to the ethoxydiglycol and mixed until the drug was completely dissolved. The polymer thickener component was added to the pharmaceutical component with mixing, immediately resulting in the formation of crystalline microparticles. Once the dispersion was homogenous, 2.0 grams of a 10% w/w aqueous sodium hydroxide solution were added to neutralize the CARBOPOL® 980 and form the gel.

The application procedures for all treatment groups were the same. Subjects applied a thin film of the study treatment onto the entire face and rubbed gently until it completely disappeared, after first washing the face with a standard cleanser. For twice-daily regimens, applications occurred once in the morning (AM) and once in the evening (PM). For once-daily regimens, applications occurred in the evening (PM). For the combination regimen, dapsone was applied in the AM and MetroGel® was applied in the PM.

Efficacy assessments included monitoring inflammatory lesion counts, Investigator Global Assessment (IGA) scores, erythema scores, and telangiectasia scores. Plasma dapsone concentrations were measured to assess systemic exposure to the study treatment. Safety was evaluated by monitoring adverse events, hematology and serum chemistry parameters, concomitant medications, vital signs, and local symptoms (dryness, itching, stinging, and burning).

Success rates, based on changes from baseline lesion counts and on the 5-point IGA, are direct indications of treatment response, and have been used in recent studies of other rosacea therapies (Wilkin et al., 2004; Thiboutot et al., 2003). Both of these endpoints are considered important and clinically relevant in evaluating the efficacy of treatments for rosacea. Erythema and telangiectasia are signs of rosacea that were evaluated according to standardized 4-point scales, and treatment-induced changes in these signs were considered to be clinically

meaningful to subjects. Subjects were followed for 7 days after stopping treatment to monitor any ongoing adverse events.

Results

Inflammatory Lesion Counts. The change from baseline in inflammatory lesion counts, percent change from baseline in inflammatory lesion counts, and lesion counts over time were summarized by N, mean, standard deviation, median, minimum, and maximum. Summaries were provided separately for each treatment group and study visit. In addition, 95% confidence intervals were provided for each treatment group and for the difference between vehicle control (VC) and each active treatment group.

The change from baseline in inflammatory lesion counts for each study visit was calculated by subtracting the baseline inflammatory lesion count from the post baseline study visit lesion counts for each subject. The percent change from baseline in inflammatory lesion counts was calculated by dividing the baseline inflammatory lesion count into the change from baseline in inflammatory lesion counts and then multiplying by 100 for each subject at each study visit.

At baseline, the mean inflammatory lesion count for all treatment groups was 21.6. Figure 1 shows the mean change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having $\geq$ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean decrease from baseline in lesion counts. Squares, vehicle control; triangles, Aczone™ (dapsone 5%) 2x/day; inverted triangles, Aczone™ (dapsone 5%) 1x/day; diamonds, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with MetroGel® alone or dapsone + MetroGel® experienced the largest mean decreases from baseline (–11.3 and –11.4 lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean decrease from baseline (–5.7 lesions from baseline). The mean change from baseline in the dapsone 2x/day group (–8.0 lesions) was higher than the dapsone 1x/day group, but similar to the VC group (–8.3 lesions), which was observed to decrease the number of inflammatory lesions.

A review of historical results for other approved therapies shows that the mean changes from baseline in lesion count for the dapsone 2x/day group was close to that of other approved products for rosacea, including Finacea® (azelaic acid) Gel, 15%, Oracea® (doxycycline) 40 mg capsules, and the active comparator in this study, MetroGel® (metronidazole), 1.0%. The changes from baseline in inflammatory lesion counts for Finacea® were reported as –10.7 and –8.9 (differences of 3.6 and 2.5 lesions in favor of active treatment over vehicle) (Finacea® package insert, 2005). For Oracea®, the changes from baseline in lesion counts were –11.8 and –9.5 (differences of 5.9 and 5.2 lesions in favor of active treatment over vehicle) (Oracea® package insert, 2006). Historically, subjects treated with the 1% strength of MetroGel® once-daily demonstrated a reduction in lesion count from baseline of –9.4 lesions, with a difference of 5.6 lesions over vehicle (MetroGel® package insert, 2005). The historical response for MetroGel® was less than the response observed in this study (–11.3 lesion decrease from baseline), which is most likely due to differences in study conditions and the fewer numbers of subjects enrolled in this study. In the intent-to-treat (ITT) analysis, treatment with the combination of MetroGel® and dapsone was not different from treatment with MetroGel® alone by Week 12 in terms of lesion count reduction.

Figure 2 shows the mean percent change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Subgroup Analysis: Subjects With <20 Lesions. The subgroup of subjects with <20 lesions at baseline was analyzed independently of the ITT group. For this subgroup, the baseline mean inflammatory lesion count ranged from 13.6 lesions to 14.3 lesions across treatment groups, with an overall mean of 14.0 lesions. Figure 3 depicts the mean change from baseline in lesion counts for this subgroup of subjects with <20 lesions at baseline. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 2x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day;

circles, Aczone™ 1x/day + MetroGel® 1x/day. Subjects in all treatment groups experienced a mean decrease from baseline in inflammatory lesion count. In this subgroup at week 12, the MetroGel® alone 1x/day experienced a mean decrease of -7.7 lesions; the dapsone + MetroGel® group experienced a mean decrease of -7.2 lesions; the vehicle control (VC) experienced a mean decrease of -6.0 lesions; and the dapsone 2x/day and dapsone 1x/day groups experienced a mean decrease of -3.6 lesions.

Figure 4 shows the mean percent change from baseline in inflammatory lesion counts in the subgroup population having <20 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with MetroGel® (metronidazole 1%) 1x/day or Aczone™ 1x/day + MetroGel® 1x/day experienced the largest mean percent decreases from baseline (55.3% and 52.0% mean reductions in lesions, respectively), while the vehicle control group experienced a 41.9% mean reduction in lesions. The dapsone 1x/day group experienced a 27.7% mean reduction in lesions and the dapsone 2x/day experienced a 23.3% mean reduction in lesions.

Subgroup Analysis: Subjects With ≥ 20 Lesions. The subgroup of subjects with ≥ 20 lesions at baseline was analyzed independently of the ITT group. The cut-off of 20 lesions was chosen as the number which most closely approximated the baseline mean lesion count in subjects who entered the study with a baseline IGA in the moderate or severe categories. The size of this subgroup was relatively large (42% of the ITT population).

For this subgroup, the baseline mean inflammatory lesion count ranged from 28.4 lesions to 33.8 lesions across treatment groups, with an overall mean of 32.1 lesions. Figure 5 depicts the mean change from baseline in lesion counts for this subgroup of subjects with ≥ 20 lesions at baseline. Squares, vehicle control; triangles, Aczone™ (dapsone 5%) 2x/day; inverted triangles, Aczone™ (dapsone 5%) 1x/day; diamonds, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. Subjects in all treatment groups experienced a mean decrease from baseline in inflammatory lesion count that

was higher than the overall mean decrease for the ITT population. In this subgroup, the dapsone 2x/day, MetroGel®, and dapsone + MetroGel® groups experienced the highest mean decreases by Week 12 (–15.5, –15.5, and –15.6 lesions respectively). The dapsone 1x/day and VC groups, respectively, experienced mean decreases of –9.3 and –11.6 lesions. Comparing the dapsone 2x/day and Vehicle Control groups, there was a 3.9 lesion difference in the mean decrease from baseline in favor of dapsone, similar to the differences between active and vehicle for other approved treatments (as described above).

Figure 6 shows the mean percent change from baseline in inflammatory lesion counts in the subgroup population having ≥ 20 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with dapsone 2x/day, MetroGel® 1x/day, and dapsone + MetroGel® experienced the largest mean percent decreases from baseline (58.4%, 46.6% and 45.0% reduction in lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean percent decrease from baseline (20.9% decrease in lesions from baseline). The mean percent change from baseline in the vehicle control group was 42.3%.

IGA Success. The IGA score and success rate from the IGA were summarized by frequencies and percents. Success rate was defined as the proportion of subjects with a score of 0 (clear) or 1 (almost clear) and at least a 2 point improvement from baseline on the 5-point Investigator's Global Assessment (IGA) scale of disease severity. In addition, 95% confidence intervals were calculated for the success rate from the IGA for each treatment group and for the difference between VC and each active treatment group.

At baseline, most subjects had an IGA score of moderate (62% for all subjects combined). The distribution of IGA scores shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. Figure 7 shows the IGA success rate over the course of the study in the intent to treat (ITT) population

having ≥ 10 inflammatory lesions. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (5.1% to 19.7%) or almost clear (25.0% to 33.8%). Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Figure 8 summarizes the IGA success rate at week 12 in the intent to treat (ITT) population having ≥ 10 inflammatory lesions. At 12 weeks, the success rate was highest in the dapsone + MetroGel® group (39.5%) and lowest in the dapsone 1x/day group (24.1%). The success rate in the dapsone 2x/day group was higher than the dapsone 1x/day group but the rate was very similar to VC (27.4% and 27.5%, respectively). The combination treatment group experienced higher success than either the MetroGel® alone (32.5%) or the dapsone 1x/day (24.1%).

Subgroup Analysis: Subjects With <20 Lesions. At baseline, 56% of the subjects with <20 lesions had a moderate score on the IGA, while 41% had a mild score on the IGA. The distribution of IGA scores in subjects with <20 lesions at baseline shifted towards improvement over the 12 weeks for all study treatments. Figure 9 shows the IGA success rate over the course of the study in subjects with <20 lesions. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At week 12, approximately 40% to 60% of the subjects enrolled in each group had an IGA score of clear (4.0% to 26.3%) or almost clear (29.8% to 42.0%).

Subgroup Analysis: Subjects With ≥ 20 Lesions. At baseline, most subjects with ≥ 20 lesions had a moderate score on the IGA (70%). Similar to the ITT analysis, the distribution of IGA scores in subjects with ≥ 20 lesions at baseline shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. Figure 10 shows the IGA success rate over the course of the study in subjects with ≥ 20 lesions. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (6.5% to 13.2%) or

almost clear (17.2% to 29.7%). Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Figure 11 summarizes the IGA success rate for this subgroup at week 12. The percentage of subjects with ≥ 20 lesions who had treatment success at Week 12 was highest in the dapsone + MetroGel® group (39.5%) and lowest in the VC group (21.2%). Success rates were better in the dapsone 2x/day group (32.3%) than either the dapsone 1x/day group (24.1%) or the VC (21.2%), equivalent to an 11.1% difference favoring dapsone 2x/day treatment. Comparing the dapsone + MetroGel® group to the MetroGel® alone group, there was a higher success rate for the combination treatment (39.5% compared to 29.7%).

Erythema assessment. Erythema assessment scores were summarized by frequencies and percents. Erythema was graded according to the standardized scale shown in Table 2, at Day 0 (baseline) and Weeks 2, 4, 8, and 12.

TABLE 2. Erythema Assessment

Score	Severity	Description
0	Absent	No perceptible erythema.
1	Mild	Slight erythema with either restricted central involvement or generalized whole face.
2	Moderate	Pronounced erythema with either restricted central involvement or generalized whole face.
3	Severe	Severe erythema or red-purple hue with either restricted central involvement or generalized whole face.

At baseline, all subjects had at least mild erythema present (16.5% to 23.8%) with the majority displaying moderate erythema (60.0% to 70.9%). In general, erythema scores improved throughout the study, with 4.8% to 9.2% of subjects exhibiting no erythema at Week 12. There were no consistent differences in the distribution of erythema scores across study treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions. For the subgroup of subjects with ≥ 20 lesions, erythema was predominantly moderate at baseline. The distribution of erythema scores tended to shift towards improvement as the study progressed in all treatment groups. By Week 12, approximately half of the

subjects in each group had improved to a score of absent (3.2% to 9.1%) or mild (31.6% to 51.4%) from mostly moderate at baseline (58.1% to 82.8%). There were no consistent differences between the treatment groups.

Telangiectasia Assessment. Telangiectasia assessment scores were summarized by frequencies and percents. Telangiectasia was graded according to the standardized scale shown in Table 3 at Day 0 (baseline) and Weeks 2, 4, 8, and 12.

TABLE 3. Telangiectasia Assessment

Score	Severity	Description
0	Absent	No perceptible telangiectasia.
1	Mild	Involvement of the nose.
2	Moderate	Involvement of the nose and infraorbital region.
3	Severe	Involvement of the nose, infraorbital region, and other areas of the face.

At baseline, telangiectasia was predominantly moderate (41.7% to 57.5% of subjects). Throughout the study, there was a small shift towards improvement of telangiectasia, demonstrated by an increase in the percentages of subjects with absent or mild telangiectasia and decreases in the percentages of subjects with moderate or severe telangiectasia. At Week 12, approximately half of the subjects in each group had either absent (13.1% to 19.7%) or mild telangiectasia (34.2% to 43.8%). There were no consistent differences in the distribution of telangiectasia scores across study treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions. At baseline, the telangiectasia score was predominantly mild in subjects with ≥ 20 lesions in the dapsone 2x/day group (51.6%) and moderate (48.3% to 63.6%) for other treatments. This pattern was still evident at Week 12; however the percentages of subjects with moderate or severe telangiectasia generally decreased while the percentages of subjects with mild or absent generally increased.

Adverse Events. Application site adverse events were the most common type of adverse event reported. The majority of application site adverse events (dryness, itching, stinging, and burning) are signs and symptoms of rosacea that were solicited and scored using the standardized grading system shown in Table 4.

TABLE 4. Local Symptoms Assessment (Dryness, Itching, Stinging, and Burning)

Score	Severity	Description
0	Absent	None
1	Mild	Barely perceptible
2	Moderate	Definitely present
3	Severe	Marked, intense

The most frequent application site adverse event was dryness, which occurred at a similar frequency among study treatment groups (32.5% to 36.7%) and was typically mild to moderate in intensity. Other application site adverse events were pain (8.0% to 29.1%), burning (10.7% to 27.8%), pruritis (8.0% to 22.8%), and erythema (9.1% to 13.9%). The frequency of these application site adverse events was numerically lower in groups treated with MetroGel® alone or MetroGel® + dapsone compared with the vehicle control or dapsone-only treated groups. For all groups, the intensity of application site pain, burning, and pruritus was mostly mild while the intensity of application site erythema was mostly moderate to severe. The higher severity of application site erythema compared with other signs/symptoms of rosacea may be explained by the presence of erythema at baseline (which was mostly moderate) as part of the underlying rosacea characteristics whereas other local signs and symptoms were mostly absent or mild.

Skin and Subcutaneous Disorders occurred at a frequency ranging from 12.0% to 20.8%. The frequency was higher in the MetroGel® group (20.8%) compared with other groups (12.0% to 17.7%). Telangectasia, reported as a worsening of baseline telangiectasia that was part of the subject's underlying rosacea, was the only adverse event to occur with a frequency higher than 1% (10.8% to 14.3%). The incidence of telangiectasia was slightly higher in groups treated with MetroGel® or MetroGel® + dapsone than the vehicle or dapsone-only treated group.

Blood plasma dapsone levels. The amounts of dapsone and metabolites N-acetyl dapsone and N-hydroxylamine dapsone in plasma were measured at baseline, Week 2, Week 4, and Week 12 of the study. Mean plasma concentrations of dapsone and metabolites were low in study treatment groups

using Aczone™ at all time points measured in the study. The highest mean plasma concentrations were observed at Week 2, where subjects had a mean dapsone concentration of 10.6 ng/mL, 7.0 ng/mL, and 6.1 ng/mL in the Aczone™ 2x/day group, Aczone™ 1x/day group, and Aczone™ + MetroGel group, respectively. The maximum plasma concentration of dapsone observed in any subject was 87.43 ng/mL, at Week 2 (Aczone™ 2x/day group). Plasma concentrations of N-acetyl dapsone were also highest at Week 2 (means of 4.9, 3.1, and 2.9 ng/mL in the Aczone™ 2x/day, Aczone™ 1x/day, and combination groups respectively). Plasma concentrations of the hydroxylamine metabolite, which is believed to be the primary factor associated with dapsone hematological toxicities, were much lower than the parent (mean values <1 ng/mL in all Aczone™-treated groups, maximum in any subject using Aczone™ 2x/day was 6.7 ng/mL).

In subjects treated with the combination of Aczone™ and MetroGel, plasma levels of dapsone and metabolites were similar to or lower than subjects treated with the same amount of Aczone™ only (1x/day), suggesting that there are no pharmacokinetic interactions between these two drugs.

Subjects with G6PD-deficiency are known to be at higher risk of developing dapsone-related hematological toxicities following oral dapsone use. In this study, 1 subject with G6PD-deficiency was enrolled and treated with Aczone™ (1x/day). When measured at Weeks 2, 4, and 12, the subject's plasma dapsone levels were approximately 11 to 12 ng/mL and hydroxylamine levels <1 ng/mL. The subject's laboratory data does not reveal any changes from baseline over the course of the study, except for slightly elevated non-fasting blood glucose at Week 4 and slightly low monocyte counts at Weeks 2 and 4 that were not deemed to be clinically significant. There were no changes in any hematological parameters. Furthermore, there were no adverse events reported indicative of systemic dapsone toxicity; only mild, transient application site adverse events were reported by this subject.

Systemic exposure to dapsone and its metabolites was low at all time points in the study. Similar mean values for hemoglobin, hematocrit, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count, total bilirubin, haptoglobin, and LDH between baseline and Week 12 were shown across all treatment groups. There were no overall changes in any

chemistry or hematology parameter observed during the study. These findings demonstrate the low incidence of systemic adverse events with topical dapsone use and support the safety of using topical dapsone, as well as dapsone in combination with MetroGel®, in subjects with papulopustular rosacea.

Discussion

The efficacy of dapsone in treating subjects with papulopustular rosacea was investigated. Two dapsone-alone dosage regimens (1x/day and 2x/day) were employed, as was a dapsone + MetroGel® regimen (1x/day). The study was controlled with the dapsone vehicle applied 2x/day (VC) and with MetroGel® alone (applied 1x/day).

Baseline characteristics were generally similar across study treatment groups, except the percentage of patients who had severe telangiectasia at baseline was more variable (6% in the Vehicle and MetroGel® groups, 20% and 15% in the dapsone 2x/day and 1x/day respectively, and 17% in the dapsone + MetroGel® group).

All treatment groups experienced a mean decrease from baseline in lesion counts. At Week 12, subjects treated with MetroGel® alone or dapsone + MetroGel® experienced the largest mean decreases from baseline in lesion counts (–11.3 and –11.4 lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean decrease from baseline (–5.7 lesions). The mean change from baseline in the dapsone 2x/day group (–8.0 lesions) was higher than the dapsone 1x/day group, but similar to the vehicle control (VC) group (–8.3 lesions).

Success rates, defined as a score of clear or almost clear with at least 2 points of improvement on a 5-point IGA scale, showed that more subjects treated with dapsone 2x/day had success (27.4%) than subjects treated with dapsone 1x/day (24.1%), but there was no difference from VC (27.5%). The success rate for the combination treatment of dapsone + MetroGel® was higher than MetroGel® alone (39.5% success rate compared with 32.5%).

Erythema and telangiectasia were evaluated, using a standardized 4-point grading system. Both erythema and telangiectasia improved, though not substantially, in all study treatment groups by Week 12. There were no apparent differences in erythema and telangiectasia between treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions At Baseline. Subjects with ≥ 20 lesions in all treatment groups experienced a greater mean decrease from baseline in inflammatory lesion count than the overall mean decrease for the ITT population having ≥ 10 inflammatory lesions and the subgroup having <20 inflammatory lesions. This result was surprising because a milder form of the disease would be expected to show similar or improved treatment results compared to a more severe form of the disease. In this subgroup of subjects with ≥ 20 lesions, the dapsone 2x/day, MetroGel®, and dapsone + MetroGel® groups experienced the highest mean decreases by Week 12 (–15.5, –15.5, and –15.6 lesions respectively, corresponding to 58.4%, 46.6% and 45.0% reductions from baseline in lesions, respectively). The VC group experienced a mean decrease of –11.6 lesions (a 42.3% decrease) and the dapsone 1x/day group experienced a mean decrease of –9.3 lesions (a 20.9% decrease in lesions from baseline) at 12 weeks. Comparing the dapsone 2x/day and VC groups, there was a 3.9 lesion difference in the mean decrease from baseline in favor of dapsone.

In the ≥ 20 lesions subgroup, success at Week 12 was highest in the dapsone + MetroGel® group (39.5%) and lowest in the VC group (21.2%). Success rates were better in the dapsone 2x/day group (32.3%) than either the dapsone 1x/day group (24.1%) or the VC group (21.2%), equivalent to an 11.1% difference favoring dapsone 2x/day treatment. Comparing the dapsone + MetroGel® group to the MetroGel® alone group, there was a higher success rate for the combination treatment (39.5% compared to 29.7%)

Systemic exposure to dapsone and its metabolites was low at all time points in the study. Treatment with dapsone was safe and well tolerated in subjects with papulopustular rosacea. Most adverse events were at the application site, were mild, and were transient. Systemic adverse events were infrequent and were generally indicative of the common cold or flu. The most frequent adverse events were application site events including dryness, pain, burning, pruritis, and erythema, which are also known signs and symptoms of rosacea.

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All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification, this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED IS:

1. A method to treat rosacea comprising topically administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

2. The method of claim 1 wherein the rosacea is papulopustular rosacea.

3. The method of claim 2 wherein the papulopustular rosacea is mild to severe papulopustular rosacea.

4. The method of claim 2 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

5. The method of claim 2 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

6. The method of claim 2 wherein treatment results in a mean reduction of at least 43 % of the papulopustular lesions.

7. The method of claim 2 wherein the patient has 20 or more inflammatory lesions.

8. The method of claim 7 wherein the pharmaceutical composition is administered twice daily.

9. The method of claim 8 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

10. The method of claim 1 wherein the rosacea is ocular rosacea.

11. The method of claim 1 wherein said pharmaceutical composition is a semisolid aqueous gel.

12. The method of claim 1 wherein said pharmaceutical composition is a cream, lotion, suspension, ointment or spray.

13. The method of claim 1 wherein the pharmaceutical composition additionally comprises a thickening agent, a high-boiling, nonionic organic solvent, a preservative, or a base agent.

14. The method of claim 1 wherein the dapsone comprises about 0.5% to 10% of the pharmaceutical composition.

15. The method of claim 1 wherein the dapsone is present in both a microparticulate state and a dissolved state.

16. The method of claim 15 wherein the microparticulate dapsone is a crystalline precipitate.

17. The method of claim 15 wherein the microparticulate dapsone is an amorphous precipitate.

18. The method of claim 1 wherein the pharmaceutical composition further comprises an antioxidant, a fragrance, a colorant, a sunscreen, or combinations thereof.

19. The method of claim 1 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide; and about 68.75% purified water.

20. The method of claim 1 further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier.

21. The method of claim 20 wherein the metronidazole is included in the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

22. The method of claim 20 wherein the metronidazole is administered separately from the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

23. The method of claim 1 wherein the pharmaceutical composition is administered twice daily.

24. A method to treat rosacea comprising topically administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier, wherein plasma levels of dapsone remain less than about 100 ng/mL.

25. The method of claim 24 wherein the rosacea is ocular rosacea.

26. The method of claim 24 wherein the rosacea is papulopustular rosacea.

27. The method of claim 26 wherein the papulopustular rosacea is mild to severe papulopustular rosacea.

28. The method of claim 26 wherein the rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

29. The method of claim 26 wherein the patient has 20 or more inflammatory lesions.

30. The method of claim 29 wherein the pharmaceutical composition is administered twice daily.

31. The method of claim 30 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

32. The method of claim 26 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

33. The method of claim 26 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

34. The method of claim 24 wherein said pharmaceutical composition is a semisolid aqueous gel.

35. The method of claim 24 wherein said pharmaceutical composition is a cream, lotion, suspension, ointment or spray.

36. The method of claim 24 wherein the pharmaceutical composition additionally comprises a thickening agent, a high-boiling, nonionic organic solvent, a preservative, or a base agent.

37. The method of claim 24 wherein the dapsone comprises about 0.5% to 10% of the pharmaceutical composition.

38. The method of claim 24 wherein the dapsone is present in a microparticulate and a dissolved state.

39. The method of claim 38 wherein the microparticulate dapsone is a crystalline precipitate.

40. The method of claim 38 wherein the microparticulate dapsone is an amorphous precipitate.

41. The method of claim 24 wherein said pharmaceutical composition further comprises an additive selected from the group consisting of an antioxidant, a fragrance, a colorant, and a sunscreen.

42. The method of claim 24 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

43. The method of claim 24 further comprising administering a composition comprising metronidazole.

44. The method of claim 43 wherein the metronidazole is included in the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

45. The method of claim 43 wherein the metronidazole is administered separately from the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

46. The method of claim 24 wherein the pharmaceutical composition is administered twice daily.

47. A method to treat papulopustular rosacea comprising topically administering to a patient having at least ten rosacea lesions an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

48. The method of claim 47, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

49. The method of claim 48, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

50. A method to treat papulopustular rosacea comprising topically administering to a patient having at least twenty rosacea lesions an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

51. The method of claim 50, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

52. The method of claim 51, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

53. The method of claim 50 wherein the pharmaceutical composition is administered twice daily.

54. The method of claim 53 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

55. The method of claim 50 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

56. The method of claim 50 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions

57. A method to treat rosacea comprising applying topically a semisolid gel composition, the semisolid gel composition comprising:

a semisolid aqueous gel; and

dapsone partially in a microparticulate form and partially dissolved in said semisolid aqueous gel.

58. The method of claim 57 wherein the rosacea is mild to severe papulopustular rosacea.

59. The method of claim 57 wherein the rosacea includes 20 or more papulopustular lesions.

60. The method of claim 59 wherein the semisolid gel composition is administered twice daily.

61. The method of claim 60 wherein the semisolid gel composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

62. The method of claim 57 wherein the rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

63. The method of claim 59 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

64. The method of claim 59 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

65. A method to treat rosacea comprising topically applying a gel composition comprising dissolved dapsone and a microparticulate dapsone, wherein:

the dissolved dapsone crosses the stratum corneum of the epidermis and is absorbed into the lower two-thirds of the pilosebaceous unit; and

the microparticulate dapsone is primarily delivered into the upper third of the pilosebaceous unit, crossing the stratum corneum of the epidermis only minimally as a solid.

66. The method of claim 65, wherein the rosacea is papulopustular rosacea.

67. The method of claim 66 wherein the papulopustular rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

68. The method of claim 66 wherein the rosacea includes 20 or more papulopustular lesions.

69. The method of claim 68 wherein the gel composition is administered twice daily.

70. The method of claim 69 wherein the gel composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

71. The method of claim 65, wherein the rosacea is ocular rosacea.

72. The method of claim 66 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

73. The method of claim 66 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

74. A method to reduce a number of papulopustular rosacea lesions comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

75. The method of claim 74 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

76. The method of claim 74, wherein the patient has at least twenty papulopustular rosacea lesions before administration of the pharmaceutical composition.

77. The method of claim 76, wherein the pharmaceutical composition is administered twice daily.

78. The method of claim 77 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

79. The method of claim 74, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

80. The method of claim 79, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered

once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

81. The method of claim 74 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

82. The method of claim 74 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

83. A method to treat mild to severe papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

84. A method to treat papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier two times daily.

85. The method of claim 84 wherein the papulopustular rosacea comprises 20 or more lesions.

86. The method of claim 85 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

87. The method of claim 84 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

88. The method of claim 84 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

89. The method of claim 84 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

90. A method to treat papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and an effective amount of a pharmaceutical composition comprising metronidazole.

91. The method of claim 90 wherein the papulopustular rosacea comprises 20 or more lesions.

92. The method of claim 91 wherein the pharmaceutical composition comprising dapsone comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

93. The method of claim 90, wherein the papulopustular rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

94. The method of claim 90 wherein the pharmaceutical composition comprising dapsone is administered once daily and the pharmaceutical composition comprising metronidazole is administered once daily.

95. The method of claim 90 wherein treatment results in a mean reduction of at least 14 papulopustular lesions.

96. The method of claim 90 wherein treatment results in a mean reduction of 43% of the papulopustular lesions.

97. A method to treat an ocular disease or disorder comprising topically administering to a patient in need thereof an effective amount of a

pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

98. The method of claim 97 wherein the ocular disease or disorder is ocular rosacea.

99. The method of claim 97 wherein the ocular disease or disorder is ocular cicatrical pemphigoid.

100. The method of claim 97 wherein the ocular disease or disorder is selected from the group consisting of conjunctivitis, scleritis, nodular scleritis secondary to Sweet's syndrome, vasculitis, autoimmune vasculitis, retinal vasculitis of Eales' disease, uveitis, granulomatous uveitis, panuveitis, ocular leprosy, arachnid evenomation, Behçet disease, linear IgA disease, relapsing polychondritis, peripheral keratitis, tuberculosis, Hodgkin lymphoma, non-Hodgkin lymphoma, T-cell lymphoma, Reiter's syndrome, tumor of the eyelid, erythema elevatum diutinum, erosive lichen planus, and pneumocystis carinii choroiditis associated with AIDS

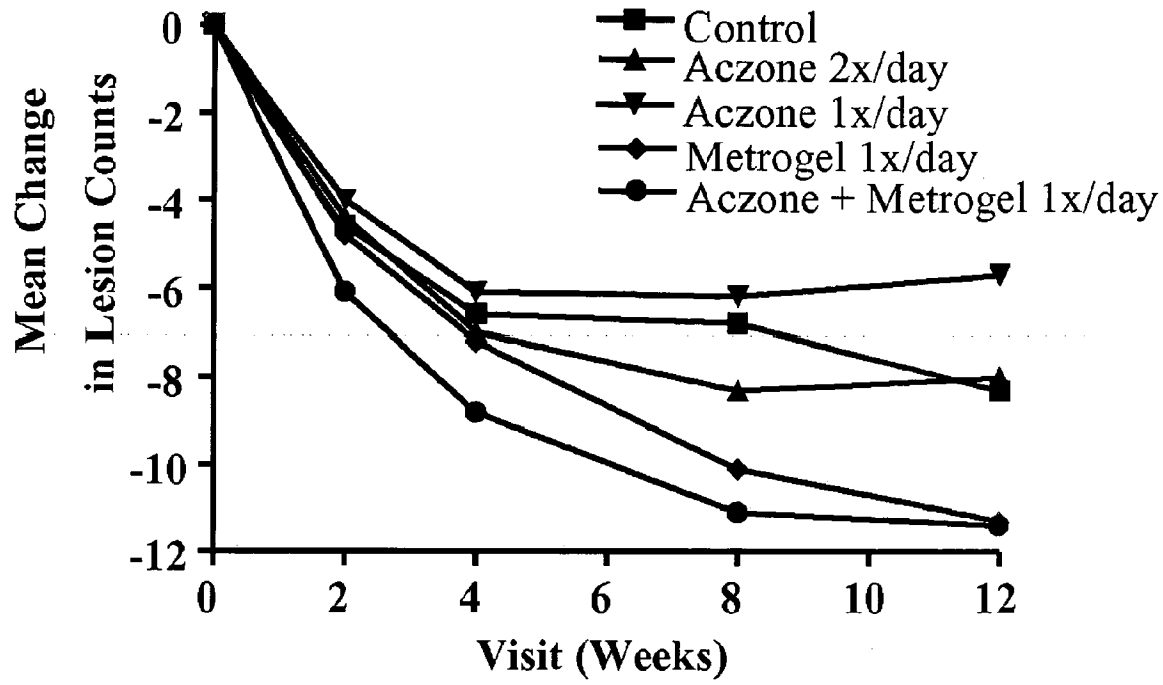

FIG. 1

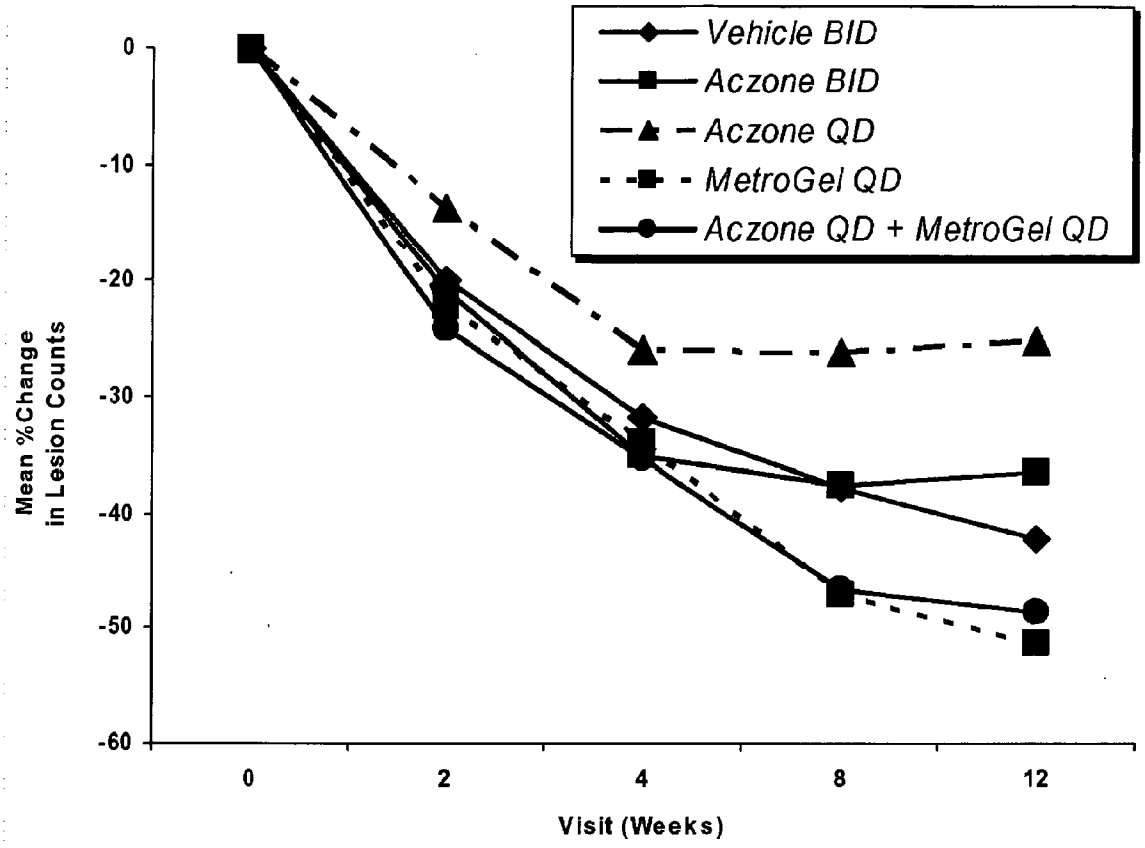

FIG. 2

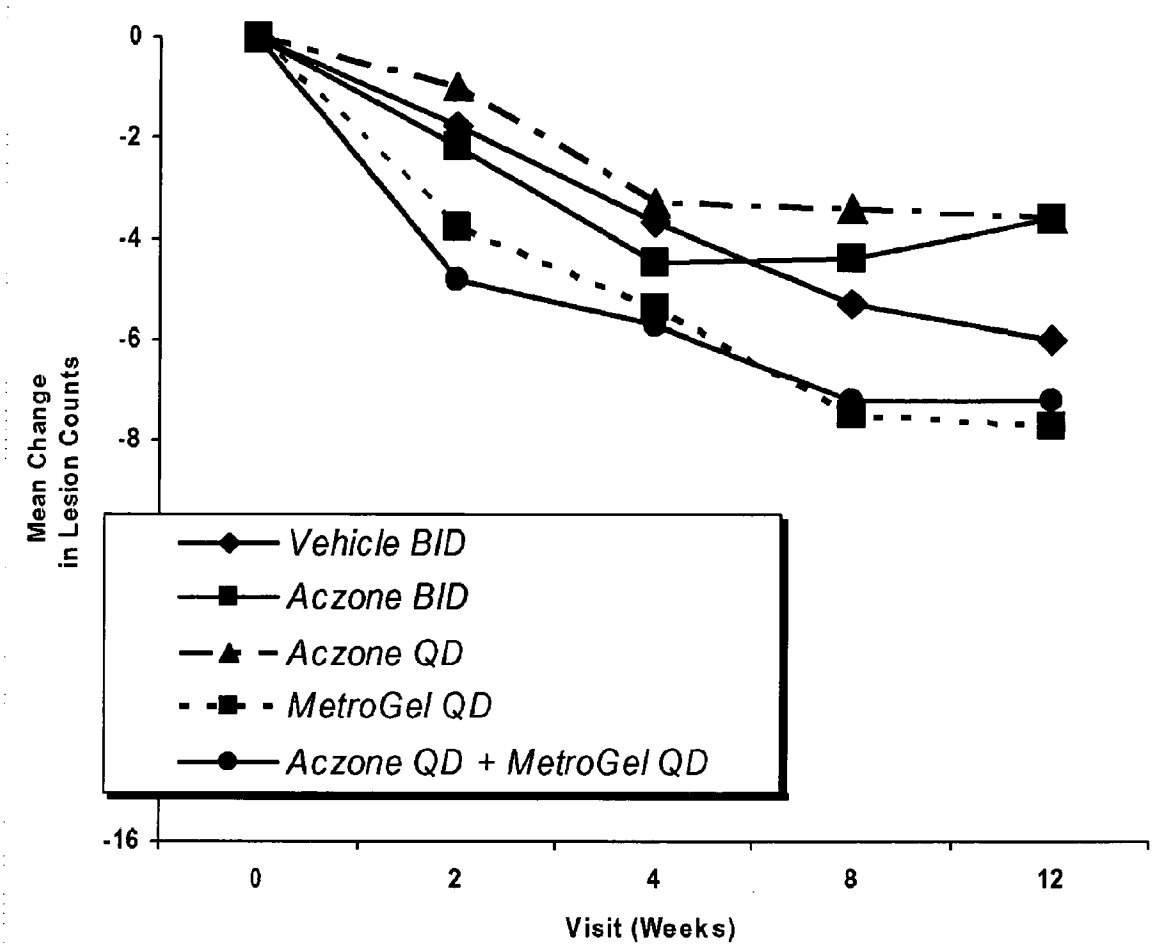

FIG. 3

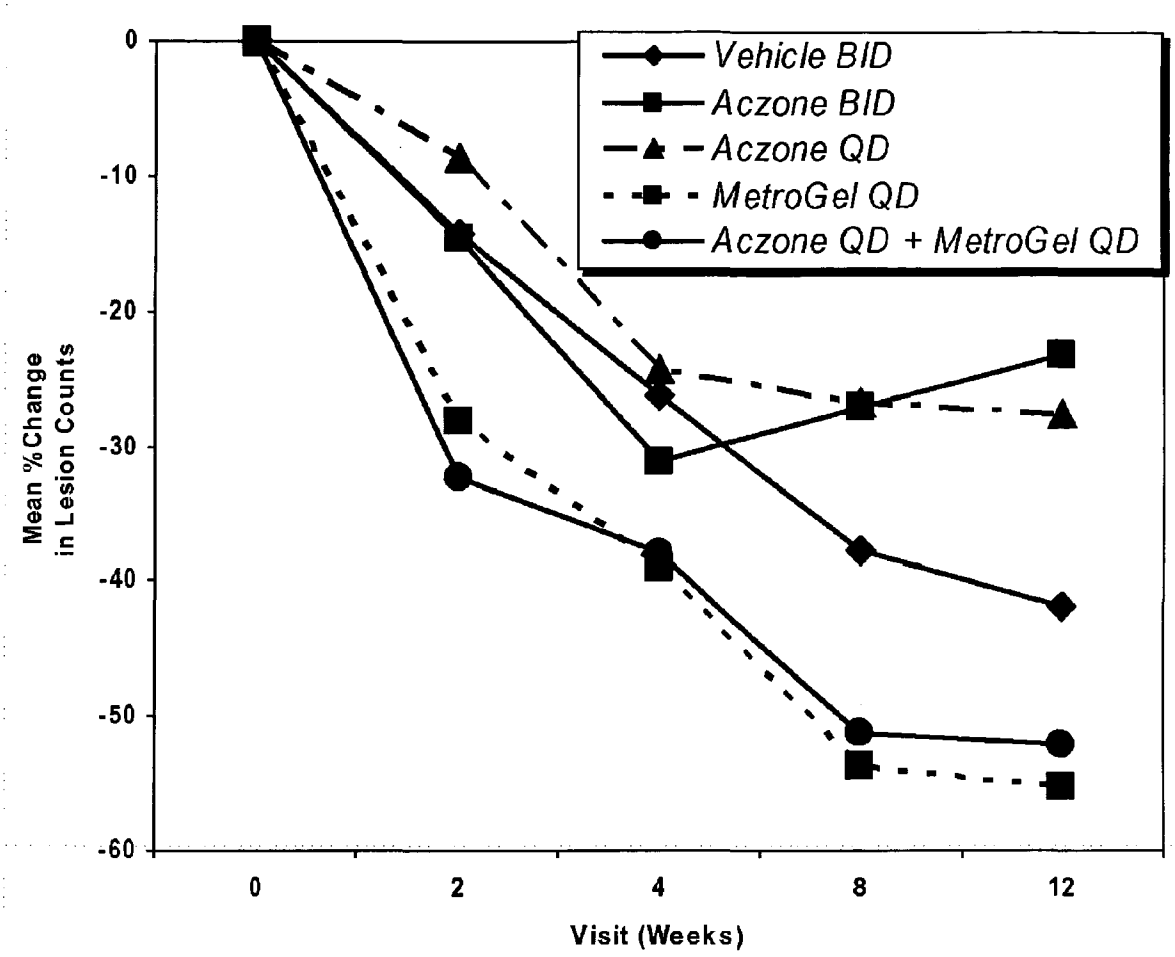

FIG. 4

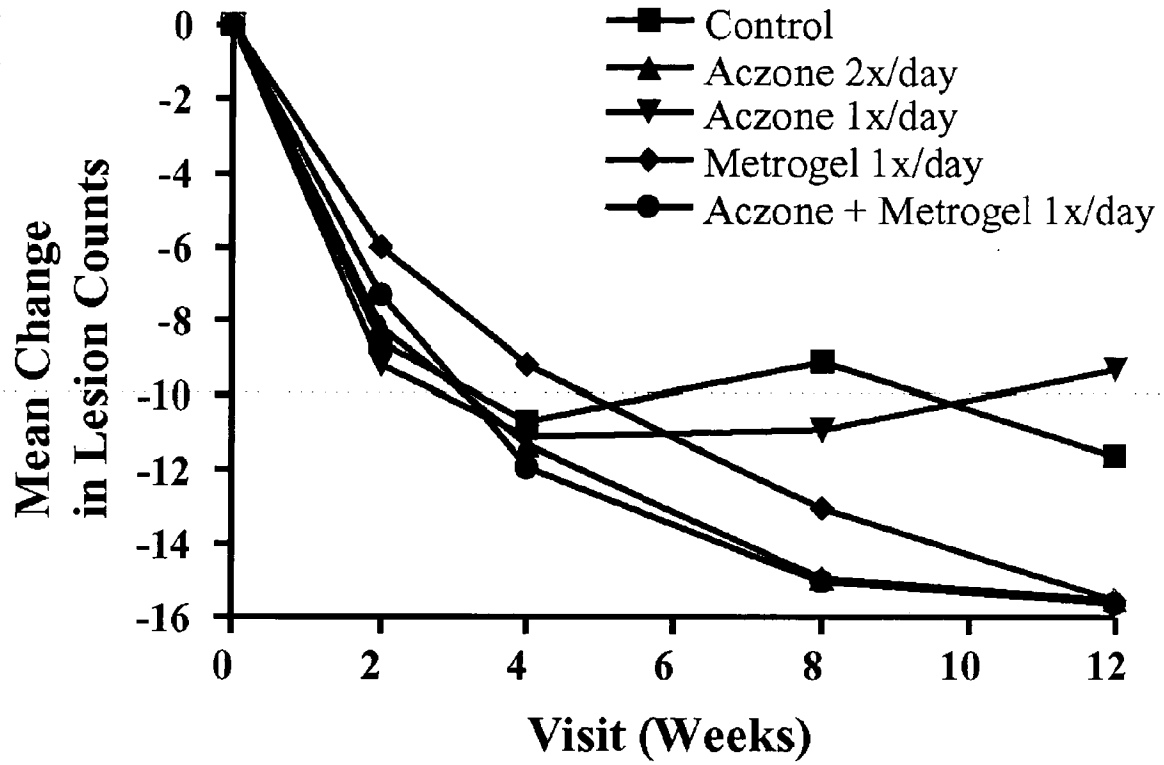

FIG. 5

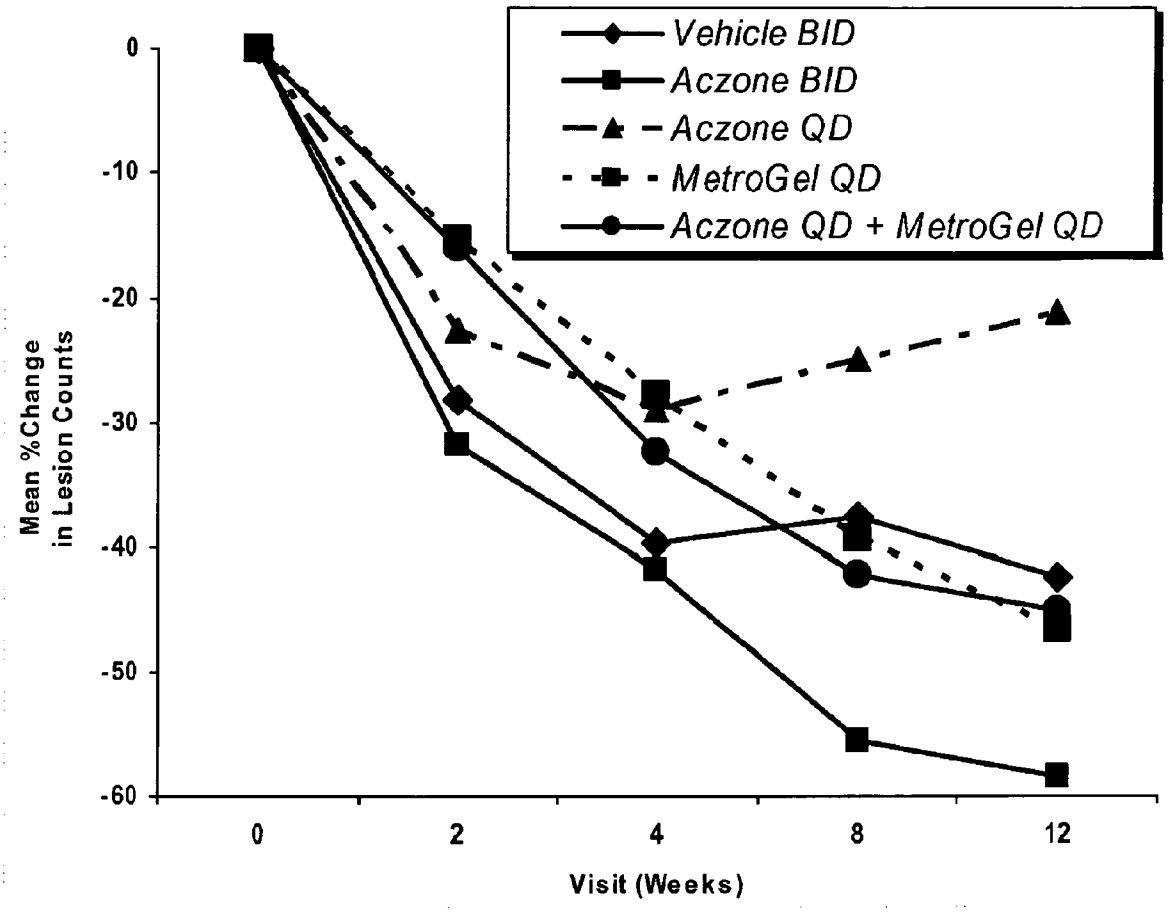

FIG. 6

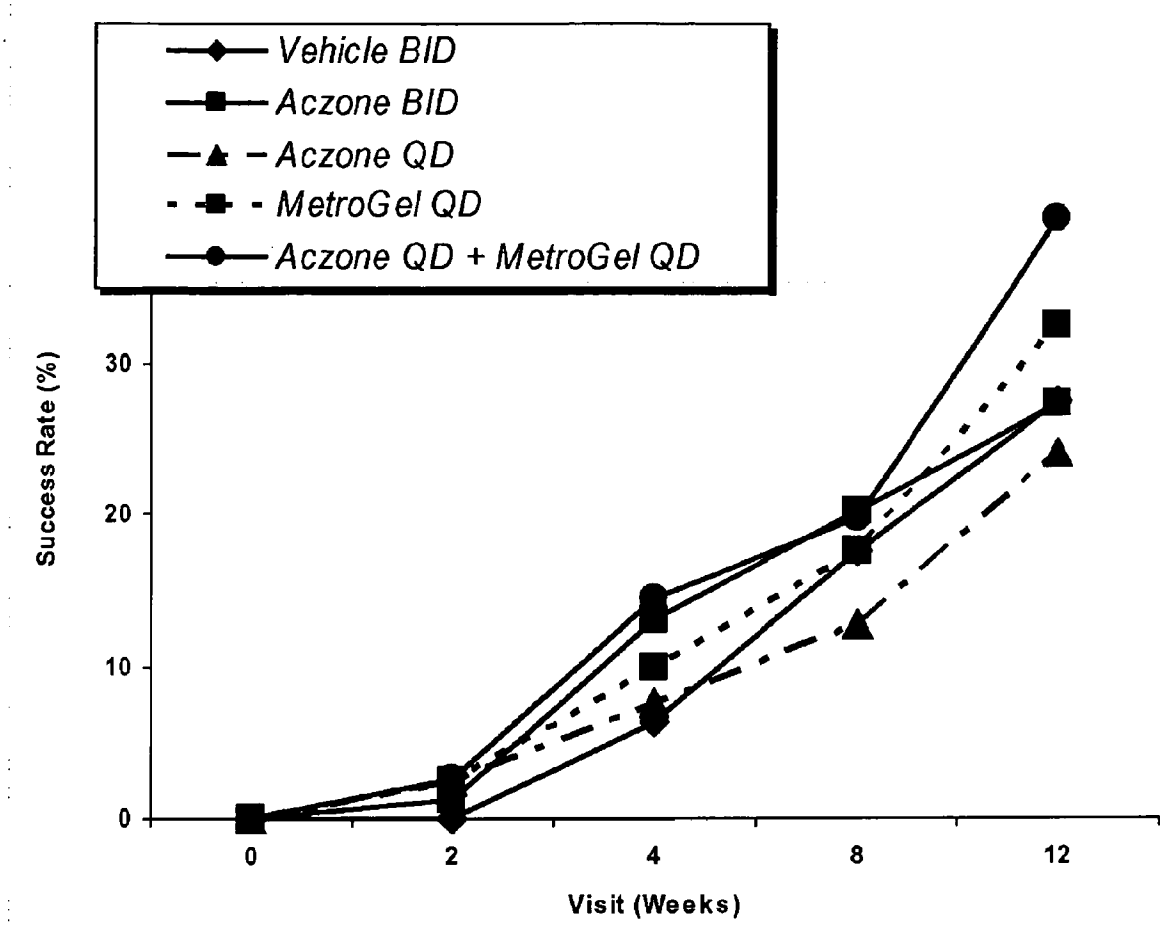

FIG. 7

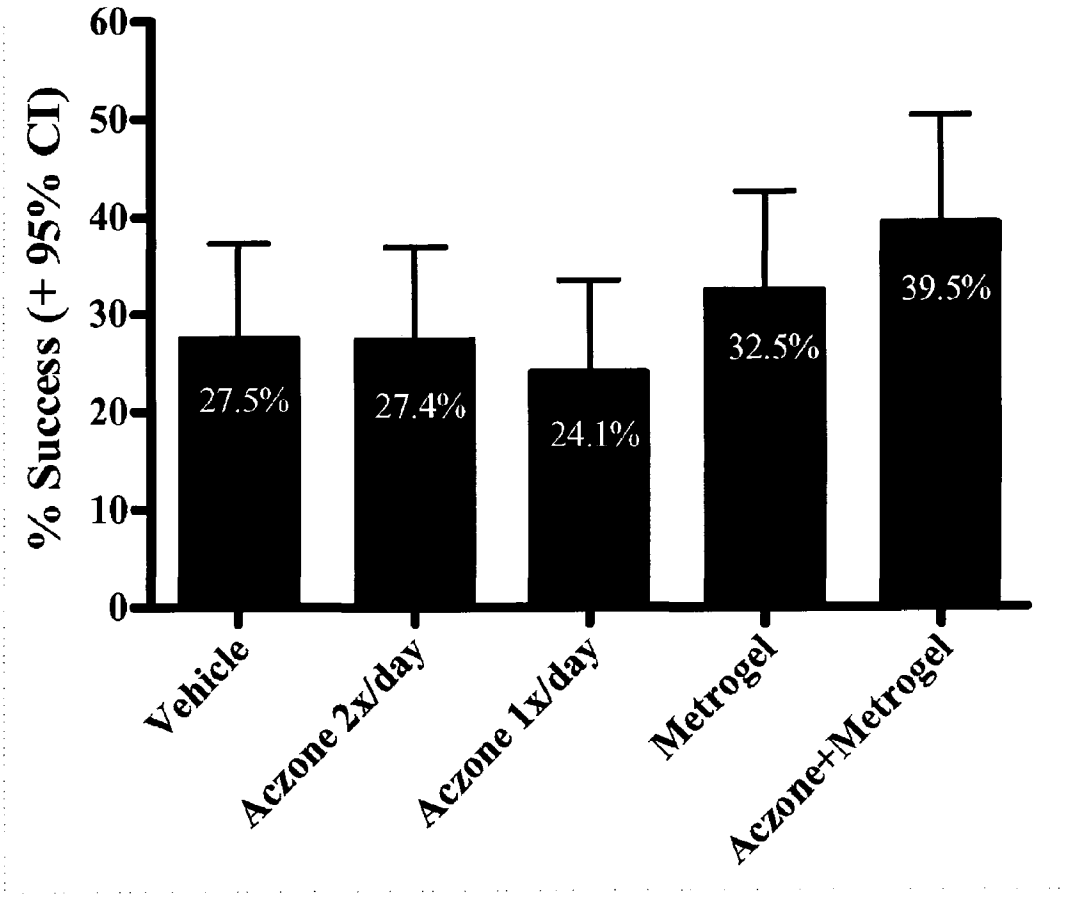

FIG. 8

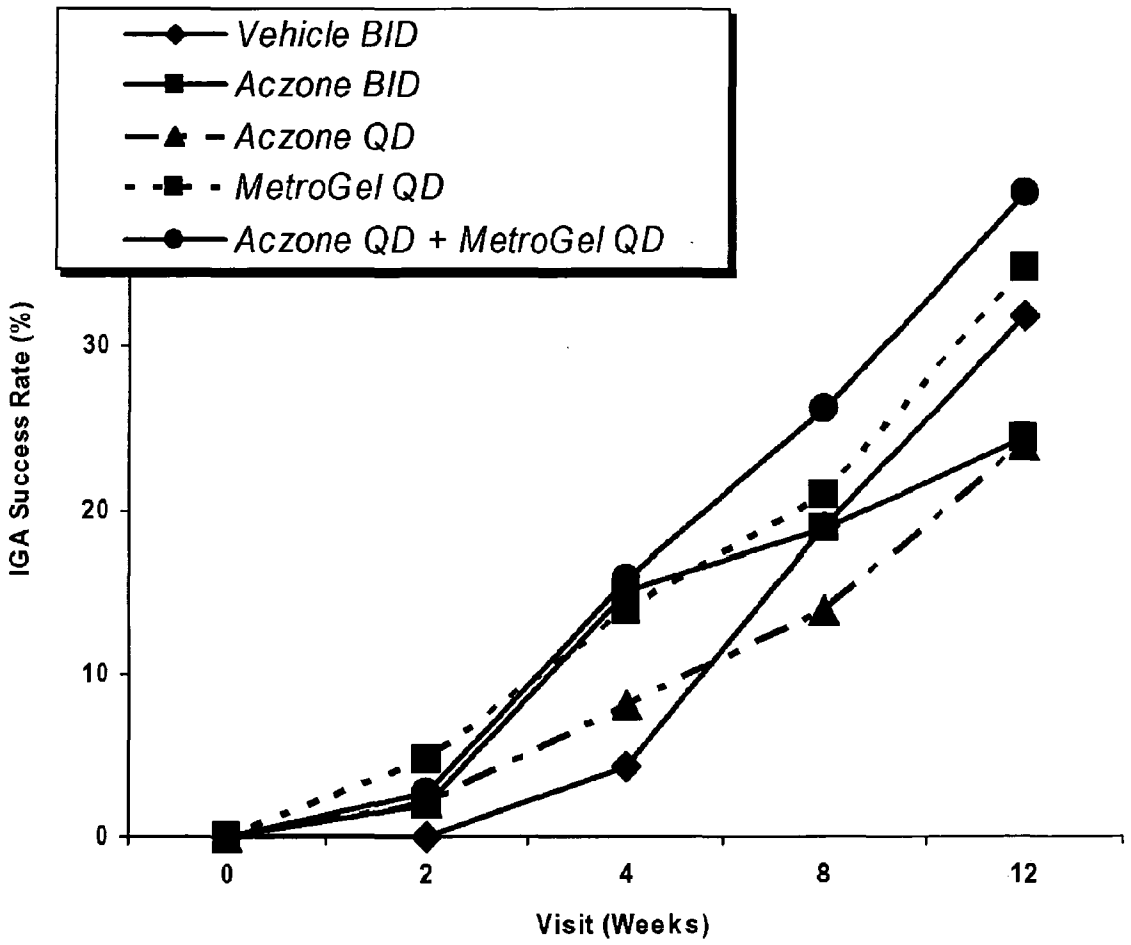

FIG. 9

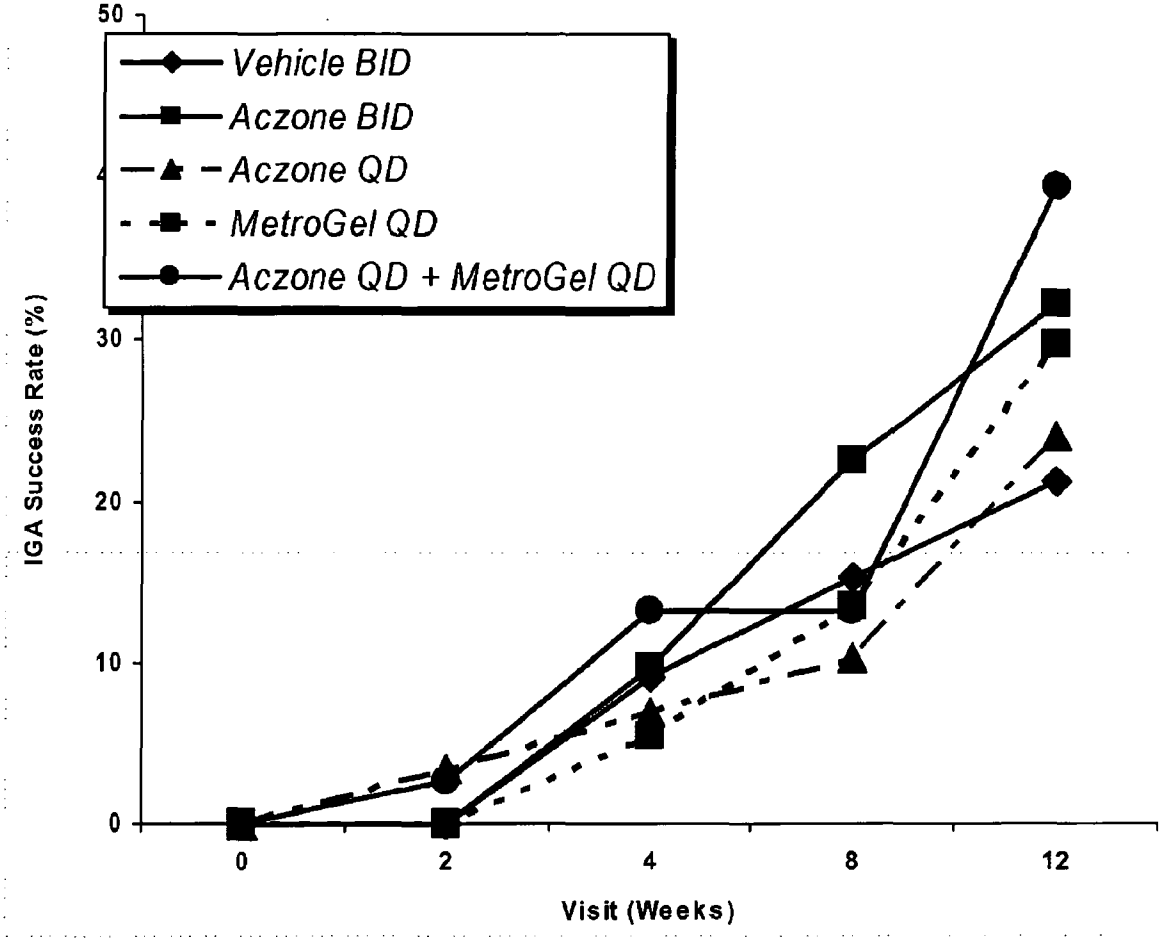

FIG. 10

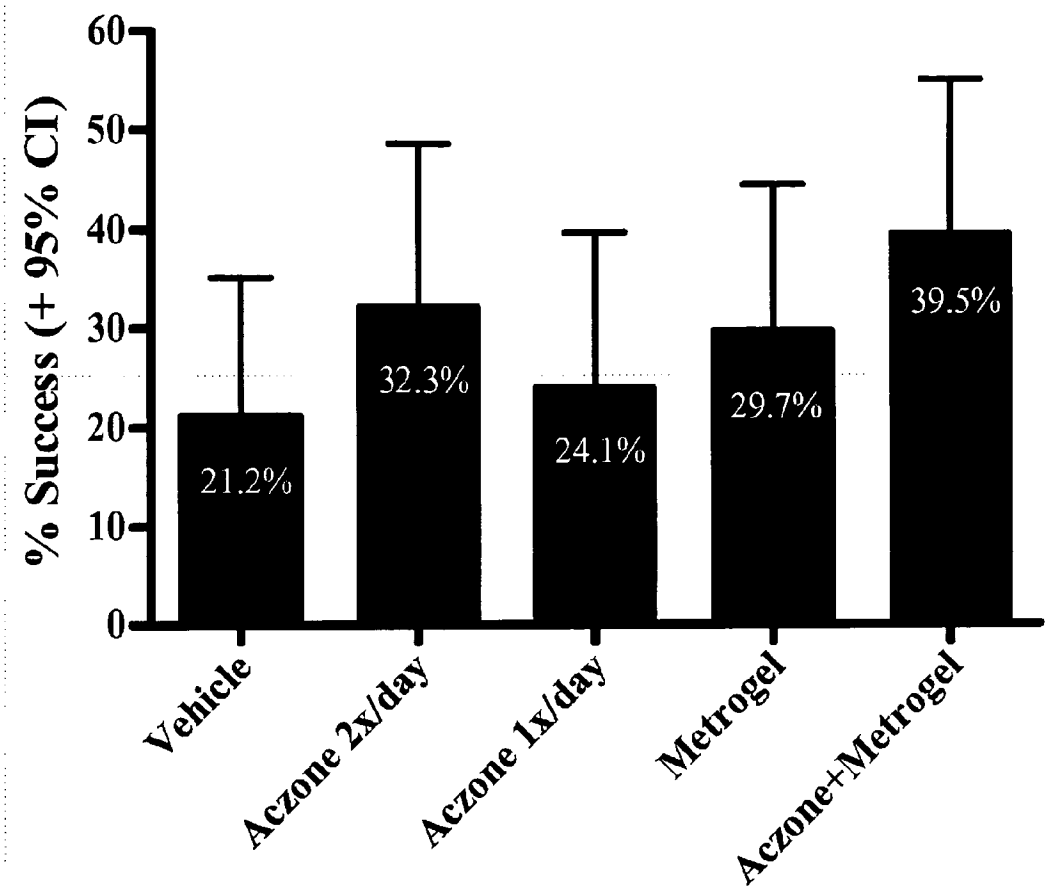

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/02549

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401, 514/170, 174, 646 - search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (USPT, PGPB, EPAB, JPAB), Google Scholar, WIPO, PubMed

Search terms - Dapsone, acne, rosacea, metronidazole, topical, papulopustular, ocular

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0122435 A1 (OSBORNE) 31 May 2007 (31.05.2007), esp para [0013], [0034], [0001]	1-89 and 91-96
Y	"UPDATE ON THE TREATMENT OF ROSACEA, A BASIC GUIDE TO CURRENT APPROACHES.", John Wolf, PRESENTATIONS FROM THE WINTER CLINICAL DERMATOLOGY CONFERENCE HELD IN MAUI, HAWAII, JANUARY 13 -17, 2006. From: http://www.skinandaging.com/supplements/pdf/wcd_1106.pdf retrived on 22 May 2008	1-89 and 98-99
X -- Y	US 2007/0281984 A1 (DOLFI et al) 06 December 2007 (06.12.2007), esp para [0010],[0037], [0038]	90 ---------- 2-10, 20-22, 25-33, 43-45, 48-49, 51-52, 55-56, 58-64, 66-73, 75-82, 85-89 and 91-96
Y	"Two Randomized Studies Demonstrate the Efficacy and Safety of Dapsone gel, 5% for the Treatment of Acne vulgaris" Z. Draelos, et al. J Am Acad Dermatology.March 2007.Vol 56, No 3, pages 439, e1 - 439 e10.esp Table II, Figure 3, Figure 3c	4-9,28-33,55-56,59-64,67-70,72-73,75-78,81-82,85-89 and 91-96
X ---- Y	WO 2005/016296 A1 (LATHROP et al) 24 February 2005 (25.02.2005), esp (page 1, ln 25-28), and (page 1, ln 25-28)	97,100 ------ 98-99

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2008 (15.05.2008)	11 JUN 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: COMBINATION OF DAPSONE WITH ADAPALENE

Fig. 1

Ingredient	Composition (% w/w)						
	1	2	2.1-a	3	4	4.1-a	5
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	25.0	5-15	5-15	13.0	-	-	-
Lactic Acid	2.0	-	-	-	-	-	-
Dimethyl Isosorbide	-	5-15	5-15	-	5-13	5-13	-
Propylene Glycol	-	-	-	10.0	10.0	10.0	-
Glycerin	-	-	-	2.0	2.0	2.0	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	-
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	-
HEC	1-4	1-4	-	-	1-2	-	-
Carbopol 980	-	-	0.5-2	0.75	-	0.5-2	0.85
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	0.2 (NaOH)
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Methylparaben	-	-	-	-	-	-	0.2
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

(57) **Abstract**: A composition suitable for topical application that contains at least two active ingredients, one of these being dapsone and one selected from the group consisting of adapalene, tazarotene and treinion for the effective treatment of acne and other dermatological conditions.

WO 2011/014627 A1

COMBINATION OF DAPSONE WITH ADAPALENE

Cross Reference

This application claims the benefit of U.S. Provisional Patent Application Serial Number 61/229,903 filed on July 30, 2009, the entire disclosure of which is incorporated herein by this specific reference.

Field of the Invention

The present invention is directed to compositions and methods for the treatment of acne vulgaris and other dermatological conditions.

Background of the Invention

Acne is the most common skin disease that affects a large number of adolescents and young adults after they reach puberty. Though not a life threatening disease, it has serious psychological impact on the patient. Chronic inflammatory acne can also result in permanent scarring of the face.

There are multiple factors that contribute to the pathogenesis of acne, these include: 1. over activity of sebum production as a result of hormonal changes at puberty; 2. colonization of *Propionibacterium acnes* (*P.acnes*) in the pilosebaceous unit; 3. hyperkeratinization or abnormal desquamation of epithelium of the upper follicle (above the sebaceous gland) that results in blockage of the pilosebaceous canal; 4. formation of inflammatory molecules as a result of the action of *P.acnes* on sebaceous lipids.

The obstruction of the pilosebaceous canal and inflammation caused by *P.acnes* created inflammatory metabolites results in the formation of comedones. Excess sebum production as a result of hormonal changes at puberty, combined with increased epithelium turnover of the upper follicle leads to formation of microcomedones which progresses to inflammatory papules and pustules in acne. The combination of lipid rich sebum and protein rich desquamated cells provides an ideal environment for the growth and activity of *P.acnes* which converts the sebaceous lipids to the inflammatory free fatty acid molecules resulting in inflammatory acne lesions. The patient can have either non-

inflammatory (open and closed comedones), inflammatory (papules and pustules) or a combination of both which most often is the case. Topical treatments are generally sufficient in most patients to control the acne lesions.

Because acne is a multifactorial condition, the marketed products work on one or more of the underlying factors contributing to acne for its treatment. There are number of prescription and over-the-counter (OTC) products available that treat acne; however, they all lack either desired efficacy or tolerability or both. Currently available products include antibiotics (topical and systemic), benzoyl peroxide, retinoids (topical and systemic), dapsone, and a number of other compounds.

The anti-acne molecule dapsone is marketed as a commercial product Aczone®. Aczone® is a 5% dapsone gel with a gritty texture due to insoluble particles of dapsone drugs. The insolubility of dapsone limits the bioavilability of dapsone upon application and its absorption through the skin and is therefore administered twice daily. At the biochemical and molecular level, dapsone exhibits an anti-inflammatory activity which provides a unique mechanism of action for this molecule in treatment of inflammatory acne lesions. However, its mechanism of action is not entirely understood. A complex combination of inflammatory pathways produce the clinical inflammation observed in acne. It is known that neutrophils significantly contribute to inflammatory acne. Dapsone is known to suppress neutrophil recruitment & local production of toxic products there by inhibiting neutrophil chemotaxis and reducing generation of oxygen free radicals. It further inhibits release of lysosomal enzymes and reduces release and bocks inflammatory effects of prostaglandins & leukotrienes. These effects results in reduction of inflammatory acne lesions. In addition to its anti-inflammatory activity, dapsone is also effective against *P. acnes*. MIC90 against *P. acnes* is 8μg/ml.

Adapalene is a third generation retinoid, which are compounds related to Vitamin A, and has been approved by the FDA for the treatment of acne. Adapalene is known to moderate inflammatory processes but its mechanism of action is also not entirely understood. Adapalene products are sold with the concentrations of 0.1% and 0.3% w/v concentrations for gels and 0.1% w/v concentration for cream. Adapalene acts on retinoid receptors and appears to be a modifier of cellular differentiation, keratinization and inflammatory processes which are involved in the pathology of *acne vulgaris*. Absorption of adapalene from either 0.1% or 0.3% gel or cream is low. In one pharmacokinetic study,

16 patients suffering from *acne vulgaris* received 0.3% adapalene gel applied to the face, chest and back which is approximately a dosage of 2 mg/cm2. Fifteen patients resulted in quantifiable (LOQ = 0.1 ng/mL) adapalene levels with a mean C_{max} of 0.553 ± 0.466 ng/mL on Day 10 of treatment. Mean $AUC_{0\text{-}24hr}$ was 8.37 ± 8.46 ng.h/mL as determined in 15 of the 16 patients on Day 10. Terminal apparent half-life, which was determined in 15 of 16 patients, ranged from 7 to 51 hours, with a mean of 17.2 ± 10.2 hours. Adapalene was rapidly cleared from plasma and was not detected 72 hours after the last application for all but one subject.

Summary of the Invention

There is an unmet consumer need for an efficacious product for the treatment of *acne vulgaris* as the currently available products for treatment of *acne vulgaris* lack the desired efficacy and/or have side effects or tolerability issues that are undesired by the subjects.

A combination acne product would provide the benefit of enhanced efficacy compared to the products containing single active agent by taking advantage of the synergistic mechanism of action of the active agents for treatment of acne. The present invention is directed to acne products with at least two active compounds and in particular are directed to dapsone and adapalene combination formulations for the use in the treatment of dermatological conditions such as *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, psoriasis, cosmetic improvement of surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, eczema, and miliaria and other dermatological conditions.

Some embodiments of the present invention include:

1) A dermatological composition comprising dapsone, adapalene, and water.

2) The dermatological composition of paragraph 1 wherein the composition comprises 5% w/w dapsone and 0.1% or 0.3% w/w adapalene and is used for the treatment of *acne vulgaris*.

3) The dermatological composition of paragraph 2 wherein the composition is 0.5% w/w dapsone and 0.3% w/w adapalene.

4) The dermatological composition of paragraph 1 wherein the composition is a gel.

5) The compositions of paragraphs 1 and 4 wherein the composition is 0.5% w/w dapsone, 0.1% w/w adapalene, 1.5% w/w benzyl alcohol, transcutol, 5 – 25% w/w PEG 400, 0.01% w/w EDTA, and 0.03% w/w citric acid. .

6) The compositions of paragraphs 1 - 5 wherein the composition further comprises hydroxyl ethyl cellulose 1 – 4% w/w.

7) The compositions of paragraphs 1 - 5 further comprising carbopol 980 at 0.5 – 2% w/w.

8) The compositions of paragraphs 1 – 7 further comprising methyl paraben.

9) The compositions of paragraphs 1 – 8 further comprising lactic acid.

10) The compositions of paragraphs 1 – 9 further comprising glycerin.

11) The composition of paragraph 5 further comprising dimethyl isosorbide in 5 – 15% w/w.

12) The composition of paragraphs 1 - 5 wherein transcutol is present in the amount of 25% w/w.

13) The compositions of paragraphs 1 – 12 wherein a buffer selected from the group consisting of NaOH, trolamine, and hycrochloric acid is added to adjust the pH.

14) The compositions of paragraphs 1 - 13 wherein the pH of the composition is 5.5.

15) The composition of paragraphs 1 - 5 further comprising 2 – 3 % hydroxyl ethyl cellulose.

16) The compositions of paragraphs 1 - 15 wherein the composition is in the form of one selected from the group consisting of a gel, emulsion, cream, liquid, paste, lotion, nanoemulsion, microemulsion, reverse emulsion and liposomal cream.

17) The compositions of paragraphs 1- 16 wherein the composition may be used for treatment of one selected from the group consisting of *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, and miliaria and other dermatological conditions.

18) A method of treating *acne vulgarus* by application of the compositions of paragraphs 1 - 17.

19) The method of treatment of paragraph 17, wherein the application is once a day.

20) The method of treatment of paragraph 17, wherein the application is twice a day.

Brief Description of the Drawings:

Fig. 1 is directed to dapsone and adapalene formulations for the treatment of dermatological conditions;

Fig. 2 is directed to variations of formulations for the treatment of dermatological conditions of Formula 1 of Figure 1;

Fig. 3A is directed to variations of formulations for the treatment of dermatological conditions of Formula 2 of Figure 1;

Fig. 3B is directed to variations of formulations for the treatment of dermatological conditions of Formula 2 of Figure 1;

Fig. 3C is directed to variations of formulations for the treatment of dermatological conditions of Formula 2.1 of Figure 1;

Fig. 3D is directed to variations of formulations for the treatment of dermatological conditions of Formula 2.1 of Figure 1;

Fig. 4A is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4B is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4C is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4D is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1; and,

Fig. 5 is directed to dapsone and adapalene formulations for the treatment of dermatological conditions.

Detailed Description of the Invention

The present invention is directed to topical compositions for treatment of dermatological conditions which contain at least two active ingredients, one of these being dapsone and the other(s) selected from the list below for an effective treatment of acne and other dermatological conditions such as rosacea.

Some broad embodiments of the invention and possible combinations are found below:

Suitable compounds that can be combined with dapsone (2 – 10% w/w) include:

1. Agents with bactericidal and/or comedolytic properties:
    a. Benzoyl peroxide (2.5 – 10% w/w); and,

b. other antimicrobial actives that are effective against *P.acnes*.

2. Agents that inhibit comedogenesis by reducing pilosebaceous canal obstruction or have keratolytic properties such as:
   a. Salicylic acid (0.5 – 3% w/w);
   b. Azelaic acid (up to 20% w/w);
   c. Sulfacetamide-sulfur (5 – 10% w/w); and,
   d. other keratolytic agents.
3. Agents that reduce sebaceous gland secretion and effect epithelial dysquamation:
   a. Retinoids:
      i. tretinoin or trans retinoic acid (0.02 – 0.1% w/w);
      ii. Tazarotene (0.05 – 0.1% w/w);
      iii. Adapalene (0.1 – 0.3% w/w); and,
      iv. additional retinoids.
4. Topical antibiotics for directly killing *P. acnes*:
   a. erythromycin (1 – 3% w/w);
   b. clindamycin (1 – 2% w/w); and,
   c. tetracycline (1 – 3% w/w).

Potential combinations that can be used:

1. Dapsone (0.01% - 10% w/w) + retinoid (0.001% - 3% w/w)
   Examples:
   a. Dapsone 5% w/w + Adapalene 0.3% w/w;
   b. Dapsone 5% w/w + tazarotene 0.1% w/w; and,
   c. Dapsone 5% w/w + tretinoin 0.1% w/w.
2. Dapsone + benzoyl peroxide:
   Examples:
   a. Dapsone 5% w/w + benzoyl peroxide 5% w/w;
3. Dapsone + antibiotic:
   Examples:
   a. Dapsone 5% w/w + clindamycin 1% w/w.
4. Dapsone + keratolytic agent
   Examples:
   a. Dapsone 5% w/w + Azelaic acid 20% w/w.

The concentration values (w/w) in parenthesis represent preferred concentration; however, other concentrations values (w/v) can be used dependent on the formulation characteristics and the desired level of efficacy and tolerability.

In a recent clinical trial the safety and efficacy of dapsone gel co-administered with adapalene gel was assessed. The study design consisted of having patients apply the product Aczone® (5% w/w dapsone) twice a day, with morning and evening application. About 10 minutes after the evening application of Aczone®, patients applied a thin layer of 0.1 % w/w adapalene gel. The 10 minute separation between applications of the two products ensured complete absorption of the Aczone® formulation into the skin to minimize the potential negative impact on adapalene or dapsone skin penetration. Application of the 0.1% w/w adapalene gel immediately after the Aczone® application may have resulted in a situation where the adapalene or dapsone would have a lower skin penetration because of the mixing of the two formulation vehicles. Further, the additional thickness of the combined formulation applications may increase the penetration distance of the two actives also resulting in reduced skin penetration of the actives.

The results of the trial showed that dapsone gel administered concurrently (but not together) with adapalene gel is safe and well tolerated for the treatment of *acne vulgaris*. One aspect of the present invention is a combination adapalene/dapsone topical formulation combining the two actives into one formulation. The novelty of this invention is in part attributable to the use of additional excipients (solubilizers) in combination with diethylene glycol monoethyl ether ("DGME") in order to solubilize dapsone. Addition of cosolvents has enabled the complete dissolution of dapsone in the formulation and an increase in the solubility of adapalene (adapalene is not completely solubilized in these formulations). The increased concentration of dissolved dapsone and adapalene versus the marketed product comparators administered concurrently will increase the rate of skin penetration of both drugs into and through the skin

Topical dosage forms of the present invention include, but are not limited to solutions, gels, creams, ointments, foams, emulsions, films, and facial/skin peels. The present invention is directed to topical dapsone and adapalene formulations which are formulated to optimize the dermal delivery profile of adapalene and dapsone to effectively treat acne and other dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin.

Examples of some formulations encompassed by the present invention excipients and concentration ranges are summarized in Table 1 below:

Table 1: Example Excipient Composition Ranges Utilized in Adapalene / Dapsone Topical Formulations:

Ingredient	Function	Composition (% w/w)
Dapsone	Active	0.5 - 10
Adapalene	Active	0.1-0.3
Carbomer 980	Thickener	0.05 – 1.5
Hydroxyethyl cellulose		1-8%
Hydroxypropyl cellulose		1-6%
NaOH	Neutralizing Agent	0.01 – 2.0
Trolamine	Neutralizing Agent	0.01 – 2.0
Ethanol	Solubilizers	1 – 90
Lactic acid		1- 10
diethylene glycol monoethyl ether		1 – 50
propylene glycol		1 – 60
Dimethyl isosorbide		1 -30
Polyethylene glycol 400		1 – 50
Hexylene glycol		1 – 50
Isostearyl alcohol		0.5 – 10
Medium chain triglycerides		0.5 – 10
Isopropyl myristate		2 – 10
Benzyl alcohol	Preservative	0.5-5
Methyl Paraben	Preservative	0.1-0.3
Propyl Paraben	Preservative	0.01-1
Benzalkonium Chloride	Preservative	0.1-0.2
Sorbic Acid	Preservative	0.1-2.7
Glycerol	Humectant	1 – 20
Polyvinyl alcohol	Film forming	1-30
Water	Vehicle	1 - 90
EDTA Disodium	Antioxidant	0.005 – 0.02
Citric Acid	Antioxidant	0.015 – 0.06
Butylated hydroxytoluene	Antioxidant	0.005 – 1
Butylated hydroxyanisole	Antioxidant	0.01 -0.25
Propyl gallate	Antioxidant	0.01 – 0.1
Elastomer 10	Thickener	0.1-90
ST Wax 30	Thickener	0.1-50
Dimethiconol blend 20	Thickener	0.1-50
Emulsifier 10	Emulsifier	0.1-50
cyclomethicone 5	Solvent	0.1-50
Silicone fluid	Solvent	0.1-50
Silky wax 10	Thickener	0.1-50

Further specific compositions of the present invention of 5% w/w dapsone and 0.1% w/w and 0.3% w/w adapalene formulations include but are not limited to:

Table 2A: Adapalene / Dapsone Topical Formulations

Ingredient	Function	Composition (% w/w)								
Dapsone	Active	5	5	5	5	5	5	5	5	5
Adapalene	Active	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%
diethylene glycol monoethyl ether	Solubilizing Agent	25	20	25	20	25	25	25	25	25
Benzyl Alcohol	Preservative	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	Solubilizing Agent	25	20	25	20	15	-	-	-	-
Lactic Acid	Solubilizing Agent	5	4	-	-	-	-	-	-	-
Dimethyl Isosorbide	Solubilizing Agent	-	-	-	-	15	-	-	-	-
Propylene Glycol	Solubilizing Agent	-	-	-	-	-	20	20	10	-
Glycerin	Humectant	-	-	-	-	-	10	10	2	-
Isopropyl Myristate	Solubilizing Agent	-	-	-	-	-	-	-	-	5
EDTA	Antioxidant	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	-

Disodium										
Citric Acid	Antioxidant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	-
Hydroxyethyl Cellulose	Thickener	4	3		-	4	-	-	-	-
Carbopol 980	Thickener	-	-	-	0.75	-	0.75	0.75	0.75	-
Hydroxypropyl Cellulose	Thickener	-	-	-	-	-	-	-	-	3
NaOH	Neutralizing Agent	1.5	1.2	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Diluted Hydrochloric Acid	Neutralizing Agent	-	-	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Ethanol	Solubilizer	-	-	-	-	-	-	-	-	60
Water	Vehicle	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	-

Table 2B, Adapalene / Dapsone Topical Formulations (cont.)

Ingredient	Function	Composition (% w/w)		
Dapsone	Active	5	5	5
Adapalene	Active	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%
diethylene glycol monoethyl ether	Solubilizing Agent	25	25	25
Benzyl Alcohol	Preservative	1.5	1.5	1.5
PEG 400	Solubilizing Agent	13	-	-
Dimethyl Isosorbide	Solubilizing Agent	-	13	13
Propylene Glycol	Solubilizing Agent	15	15	15
Glycerin	Humectant	2	2	2
EDTA Disodium	Antioxidant	0.01	0.01	0.01
Citric Acid	Antioxidant	0.03	0.03	0.03
Hydroxyethyl Cellulose	Thickener	-	2	-
Carbopol 980	Thickener	0.75	-	-
Hydroxypropyl Cellulose	Thickener	-	-	2
NaOH	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Water	Vehicle	q.s.a.d.	q.s.a.d.	q.s.a.d.

The formulations of the present invention can be made as follows based on the excipients:

Process for making lactic acid containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, lactic acid, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;

b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;

c. Add adapalene to mixture in step b;

d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,

e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making DMI / hydroxyethyl cellulose containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, dimethyl isosorbide, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;

b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved.

c. Add adapalene to mixture in step b;

d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,

e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making DMI / Carbopol containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, dimethyl isosorbide, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;

b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;

c. Add adapalene to mixture in step b;

d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,

e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/PEG containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/DMI/Carbopol containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, dimethyl isosorbide, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/DMI/HEC containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, dimethyl isosorbide, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,

e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

The most effective dapsone and adapalene composition is selected based on clinical studies. For example, a clinical study is conducted by forming two treatment groups, one with daily application of a selected dapsone and adapalene formulation, and twice daily topical application of the same selected dapsone and adapalene formulation to the acne area of the skin for a period of 12 weeks. Two control groups are formed with application once and twice daily of a vehicle consisting of the same excipients but no active ingredients. The patient's inflammatory and non-inflammatory acne lesion counts should be recorded at baseline before initiation of treatment and then at select intervals throughout the study. The reduction in total, non-inflammatory or inflammatory lesions counts provides determination of the efficacy of the formulations. The established Global Acne Assessment Score (GAAS) should be used to assess efficacy of the product. The tolerability of the product can be determined by assessment of skin dryness, irritation, sensitivity and redness as a result of treatment. A product is considered to have better tolerability if there is less effect on these parameters.

Application method:

1. A suitable application method is topical cream, gel, lotion, ointment, foam, liquid or a semi solid preparation. A topical preparation may contain additional ingredients to provide aesthetic and moisturizing and anti-inflammatory benefits to the skin. Generally,
    a. A gel or liquid preparation can be alcohol or aqueous based or a combination of two;
    b. A nanoemulsion or microemulsion preparation can be used for enhanced delivery of actives;
    c. A liposomal cream or lotion preparation can be used for enhanced delivery of actives; and
    d. A foam preparation can be a quick breaking foam with additional emollient components.
2. Topical preparations that result in slow release or controlled release of the active agent can also be used to provide an optimal efficacy and tolerability balance.

3. Active ingredients encapsulated in micro beads or adsorbed on microsponge can be used for control release and in addition solve any incompatibility issues between the formulation ingredients.
4. The application is preferably once a day or more frequent depending on the desired effect.

Application of the formulations of the present invention:

Example #1 – Application of 0.1% w/w adapalene of Formula 1 in Fig. 5

A 17 year old Caucasian male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #1 in Fig. 5. The 17 year old male patient applies the 0.1% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 17 year old male patient experiences a 32% reduction in inflammatory and non-inflammatory lesions.

Example #2 - Application of 0.3 % w/w adapalene of Formula 1 in Fig. 5

A 16 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #1 in Fig. 5. The 16 year old female patient applies the 0.3% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 16 year old female patient experiences a 41% reduction in inflammatory and non-inflammatory lesions.

Example #3 – Application of 0.1% w/w adapalene of Formula 2 in Fig. 5

A 23 year old African-American female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #2 in Fig. 5. The 23 year old female patient applies the 0.1% w/w adapalene composition of Formula 2 once daily for 12 weeks. After 12 weeks, the 23 year old female patient experiences a 24 % reduction in inflammatory and non-inflammatory lesions.

Example #4 – Application of 0.3% w/w adapalene of Formula 2 in Fig. 5

A 19 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #2 in Fig. 5. The 19 year old female patient

applies the 0.3% w/w adapalene composition of Formula 2 once daily for 12 weeks. After 12 weeks, the patient experiences a 248 % reduction in inflammatory and non-inflammatory lesions.

Example #5 – Application of 0.1% w/w adapalene of Formula 3 in Fig. 5

A n 18 year old African-American male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #3 in Fig. 5. The 18 year old male patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the 18 year old male patient experiences a 29 % reduction in inflammatory and non-inflammatory lesions.

Example #6 – Application of 0.3% w/w adapalene of Formula 3 in Fig. 5

A n 23 year old Asian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #3 in Fig. 5. The 23 year old patient applies the 0.3% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the patient experiences a 25 % reduction in inflammatory and non-inflammatory lesions.

Example #7 – Application of 0.1% w/w adapalene of Formula 4 in Fig. 5

An 18 year old African-American male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #3 in Fig. 5. The 18 year old male patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the 18 year old male patient experiences a 29 % reduction in inflammatory and non-inflammatory lesions.

Example #8 – Application of 0.3% w/w adapalene of Formula 4 in Fig. 5

A 17 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #4 in Fig. 5. The 17 year old male patient applies the 0.3% w/w adapalene composition twice daily for 12 weeks. After 12 weeks, the 17 year old male patient experiences a 41 % reduction in inflammatory and non-inflammatory lesions.

Example #9 – Application of 0.1% w/w adapalene of Formula 5 in Fig. 5

A 16 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #5 in Fig. 5. The 16 year old female patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the patient experiences a 27 % reduction in inflammatory and non-inflammatory lesions.

Example #10 - Example #9 – Application of 0.3% w/w adapalene of Formula 5 in Fig. 5

A 19 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #5 in Fig. 5. The 19 year old female patient applies the 0.3% w/w adapalene composition twice daily for 12 weeks. After 12 weeks, the patient experiences a 38 % reduction in inflammatory and non-inflammatory lesions.

Example #11 – Application of 0.1% w/w adapalene of Formula 1 in Fig. 5

A 37 year old Caucasian male patient suffers from rosacea and applies a 0.1% w/w adapalene formulation according to formulation #1 in Fig. 5. The 37 year old male patient applies the 0.1% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 37 year old male patient experiences a reduction in the symptoms of rosacea.

Claims:

1) A dermatological composition comprising dapsone, adapalene, and water.

2) The dermatological composition of claim 1 wherein the l composition comprises 5% w/w dapsone and 0.1% w/w adapalene and is used for the treatment of *acne vulgaris*. .

3) The dermatological composition of claim 2 wherein the composition is 0.5% w/w dapsone and 0.3% w/w adapalene.

4) The dermatological composition of claim 1 wherein the composition is a gel.

5) The composition of claim 1 wherein the composition is 0.5% w/w dapsone, 0.1% w/w adapalene, 1.5% w/w benzyl alcohol, transcutol, 5 – 25% w/w PEG 400, 0.01% w/w EDTA and 0.03% w/w citric acid. .

6) The composition of claim 5 wherein the composition further comprises hydroxyl ethyl cellulose 1 – 4% w/w.

7) The composition of claim 5 further comprising carbopol 980 at 0.5 – 2% w/w.

8) The composition of claim 5 further comprising methyl paraben.

9) The composition of claim 5 further comprising lactic acid.

10) The composition of claim 5 further comprising glycerin.

11) The composition of claim 5 further comprising dimethyl isosorbide at 5 – 15% w/w.

12) The composition of claim 5 wherein transcutol is present in the amount of 25% w/w.

13) The composition of claim 5 wherein a buffer selected from the group consisting of NaOH, trolamine, and hycrochloric acid is added to adjust the pH.

14) The composition of claim 13 wherein the pH of the composition is 5.5.

15) The composition of claim 5 further comprising 2 – 3 % hydroxyl ethyl cellulose.

16) The composition of claim 1 wherein the composition is in the form of one selected from the group consisting of a gel, emulsion, cream, liquid, paste, lotion, nanoemulsion, microemulsion, reverse emulsion and liposomal cream.

17) The composition of claim 5 wherein the composition may be used for treatment of one condition selected from the group consisting of *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, and miliaria and other dermatological conditions.

18) A method of treating *acne vulgarus* by application of the composition of claim 1.

19) The method of treatment of claim 17, wherein the application is once a day.

20) The method of treatment of claim 17, wherein the application is twice a day.

Fig. 1

Ingredient	Composition (% w/w)						
	1	2	2.1-a	3	4	4.1-a	5
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	25.0	5-15	5-15	13.0	-	-	-
Lactic Acid	2.0	-	-	-	-	-	-
Dimethyl Isosorbide	-	5-15	5-15	-	5-13	5-13	-
Propylene Glycol	-	-	-	10.0	10.0	10.0	-
Glycerin	-	-	-	2.0	2.0	2.0	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	-
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	-
HEC	1-4	1-4	-	-	1-2	-	-
Carbopol 980	-	-	0.5-2	0.75	-	0.5-2	0.85
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	0.2 (NaOH)
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Methylparaben	-	-	-	-	-	-	0.2
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 2

Ingredient	Composition (% w/w)						
	1	**1-a**	**1-b**	**1-c**	**1-d**	**1-e**	**1-f**
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Lactic Acid	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Dimethyl Isosorbide	-	-	-	-	-	-	-
Propylene Glycol	-	-	-	-	-	-	-
Glycerin	-	-	-	-	-	-	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	1	1.5	2	2.5	3	3.5	4
Carbopol 980	-	-	-	-	-	-	-
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 3A

Ingredient	Composition (% w/w)						
	2	2-a	2-b	2-c	2-d	2-e	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	10	15	5	10	15	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	1	1	1	2	2	2	
Carbopol 980	-	-	-	-	-	-	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 3B

Ingredient	Composition (% w/w)						
	2-f	2-g	2-h	2-i	2-j	2-k	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	10	15	5	10	15	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	3	3	3	4	4	4	
Carbopol 980	-	-	-	-	-	-	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 3C

Ingredient	Composition (% w/w)						
	2.1-a	2.1-b	2.1-c	**2.1-d**	2.1-e	2.1-f	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	5	5	5	5	5	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	-	-	-	-	-	-	
Carbopol 980	0.5	0.5	0.5	1	1	1	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 3D

Ingredient	Composition (% w/w)						
	2.1-g	2.1-h	2.1-i	**2.1-j**	2.1-k	2.1-l	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	5	5	5	5	5	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	-	-	-	-	-	-	
Carbopol 980	1.5	1.5	1.5	2	2	2	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 4A

Ingredient	Composition (% w/w)							
	4	4-a	4-b	4-c	4-d	4-e	4-f	4-g
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	8	10	13	5	8	10	13
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	1	1	1	1	1.5	1.5	1.5	1.5
Carbopol 980	-	-	-	-	-	-	-	-
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 4B

Ingredient	Composition (% w/w)							
	4-h	4-i	4-j	4-k	4.1-a	4.1-b	4.1-c	4.1-d
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	8	10	13	5	6	7	8
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	2	2	2	2	-	-	-	-
Carbopol 980	-	-	-	-	0.5	0.5	0.5	0.5
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 4C

Ingredient	Composition (% w/w)							
	4.1-e	**4.1-f**	4.1-g	4.1-h	**4.1-i**	**4.1-j**	4.1-k	4.1-l
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	6	7	8	5	6	7	8
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	-	-	-	-	-	-	-	-
Carbopol 980	1	1	1	1	1.5	1.5	1.5	1.5
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 4D

Ingredient	Composition (% w/w)							
	4.1-m	4.1-n	4.1-o	4.1-p				
Dapsone	5.0	5.0	5.0	5.0				
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3				
Transcutol® P	25.0	25.0	25.0	25.0				
Benzyl Alcohol	1.5	1.5	1.5	1.5				
PEG 400	-	-	-	-				
Lactic Acid	-	-	-	-				
Dimethyl Isosorbide	5	6	7	8				
Propylene Glycol	10.0	10.0	10.0	10.0				
Glycerin	2.0	2.0	2.0	2.0				
EDTA Disodium	0.01	0.01	0.01	0.01				
Citric Acid	0.03	0.03	0.03	0.03				
HEC	-	-	-	-				
Carbopol 980	2	2	2	2				
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5				
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5				
Methylparaben	-	-	-	-				
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.				

Fig. 5

Ingredient	Function	Composition (% w/w)				Aczone + adapalene
Formulation #		**1**	2	3	4	**5**
Dapsone	Active	5	5	5	5	5
Adapalene	Active	0.1% and 0.3%	0.1% and 0.3%	0.1% and 0.3%	0.1% and 0.3%	0.1% and 0.3%
transcutol	Solubilizing Agent	25	25	25	25	25
Benzyl Alcohol	Preservative	1.5	1.5	1.5	1.5	
PEG 400	Solubilizing Agent	25	15	13		
Lactic Acid	Solubilizing Agent	5	-			
Dimethyl Isosorbide	Solubilizing Agent	-	15		13	
Propylene Glycol	Solubilizing Agent	-	-	15	15	
Glycerin	Humectant	-	-	2	2	
EDTA Disodium	Antioxidant	0.01	0.01	0.01	0.01	
Citric Acid	Antioxidant	0.03	0.03	0.03	0.03	
Hydroxyethyl Cellulose	Thickener	4	4		2	
Carbopol 980	Thickener	-	-	0.75		0.85
NaOH	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	0.2
Diluted Hydrochloric Acid	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methyl paraben	Preservative	-	-	-	-	0.2
Water	Vehicle	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/043671

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/06 A61K31/136 A61K31/192 A61K9/00 A61P17/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4%, or vehicle gel for the treatment of acne vulgaris: A randomized, double-blind study" JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, C.V. MOSBY, ST. LOUIS, MO, US, vol. 56, no. 2, 1 February 2007 (2007-02-01), page AB16, XP005936732 ISSN: 0190-9622 the whole document	1-20
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2010	04/11/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Young, Astrid

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/043671

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search (PALM Database, eDAN, EAST)	11/11/15	LARD
EAST Search (See Attached Search History)	11/11/15	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	11 November 2015

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	9352	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:26
S2	24577	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:27
S3	253562	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:28
S4	18	S1 and S2 and S3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:28
S5	18	S4 and (water aqueous (purified adj water))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:28
S6	26368	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:29
S7	18	S1 and S3 and S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:29
S8	0	S7 not S5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:30
S9	60	S1 and S2 and (water aqueous (purified adj water)) and (methyl adj2 paraben)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:30
S10	55	S9 and (acne (acne adj2 vulgaris))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:31
S11	7	S4 and (methyl adj2 paraben)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:31
S12	36	S10 and (@pd<="20121120" @ad<="20121120")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/11/11 10:32

S13	58	(warner-kevin$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:34
S14	18	(parashar-ajay$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:34
S15	5	(swaminathan-vijaya$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:34
S16	4	(bhatt-varsha$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:34
S17	4139	(allergan$).as. (allergan$).aanm. (allergan$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:35
S18	74	S13 S14 S15 S16	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:35
S19	5	S18 and S1	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:35
S20	66	S17 and S1	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:38
S21	9	S20 and S2	US-PGPUB; USPAT; USOCR	OR	ON	2015/11/11 10:38

EAST Search History (Interference)

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11/11/2015 10:52:28 AM
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)

CONFIRMATION NO. 9004

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
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PUBLICATION NOTICE

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Title:TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

Publication No.US-2016-0030580-A1
Publication Date:02/04/2016

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kevin S. Warner, et al.	)	Group Art Unit: 1629
Serial No.:	14/885,805	)	Examiner: Draper, Leslie A. Royds
Filed:	October 16, 2015	)	Conf. No.: 9004
For:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	)	

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

This is filed in response to an Office Action mailed on November 18, 2015. Please amend the above referenced patent application as follows. Authorization is hereby given to charge any fee required for the filing of this paper, to Deposit Account No. 01-0885.

Amendments to the Claims are reflected in the **listing of claims** which begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

Amendments to the Claims:

The following claims replace all claims previously submitted in this application. Only those claims being amended herein show their changes in highlighted form, where insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g. ~~deletions~~ or [[deletions]]).

1. (**Currently Amended**) A method for treating a dermatological condition comprising administering to a subject having the dermatological condition ~~in need thereof~~ a topical pharmaceutical composition comprising:

   about 7.5% w/w dapsone;

   about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

   about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

   water;

   wherein the topical pharmaceutical composition does not comprise adapalene.

2. (Original) The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. (Original) The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. (Original) The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. (**Currently Amended**) The method of claim 1 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, ~~treatment of chronic wounds,~~ bed sores, keratosis pilarispiralis, sebaceous cysts, ~~inflammatory dermatoses,~~ post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, ~~dermatitis, eczema,~~ or miliaria.

6. (**Currently Amended**) The method of claim 5 wherein the condition is selected from the group consisting of acne vulgaris and rosacea.

7. (**Currently Amended**) A method for treating a dermatological condition comprising administering to a subject having the dermatological condition ~~in need thereof~~ a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

8. (Original) The method of claim 7, wherein the topical pharmaceutical composition further comprises methyl paraben.

9. (**Currently Amended**) The method of claim 7 wherein the dermatological condition is acne vulgaris, rosacea, atopic dermatitis, ~~treatment of chronic wounds,~~ bed sores, keratosis pilaris ~~piralis~~, sebaceous cysts, ~~inflammatory dermatoses,~~ post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, ~~dermatitis, eczema,~~ or miliaria.

10. (**Currently Amended**) The method of claim 9 wherein the condition is selected from the group consisting of acne vulgaris and rosacea.

11. (**New**) The method of claim 6 wherein the condition is acne vulgaris.

12. (**New**) The method of claim 10 wherein the condition is acne vulgaris.

REMARKS

This Reply responds to the Office Action sent November 18, 2015, in which the Office Action rejected Claims 1-10. Claims 1, 5-7, and 9-10 have been amended. Claims 11 and 12 are new. Thus Claims 1-12 are currently pending. No new matter has been added by this amendment, and all amendments to the claims are fully supported by the originally filed specification and claims. The Applicants respectfully submit that the claims are in condition for allowance.

Objections to the Claims

Claims 5 and 9 were objected to for reciting "eczema" twice in the claims and for misspelling the term "pilaris" as "piralis". The Applicants submit that the amendments to the claims submitted herewith render the objections to Claims 5 and 9 moot.

Claim Rejections

35 U.S.C. § 112(a)

Claims 1-5 and 7-9 were rejected under 35 U.S.C § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any other dermatological condition.

The Applicants submit that all of the pending claims comply with the enablement requirement. According to the MPEP, the test for enablement requires analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. *See* MPEP § 2164. The Applicants submit that the disclosure contains sufficient information regarding the subject matter of the claims. The disclosure of the present application clearly states that compositions described in the application are effective in treating dermatological conditions, including, but not limited to those recited in Claims 5 and 9. *See* the present application specification as originally

filed at paragraphs [009], [0018], [0040] and [0024]. Since the disorders being treated by the claimed methods are disclosed in the application as specifically tied to the compositions and formulations described therein, sufficient information regarding the subject matter of the claims exists so as to enable one skilled in the art to make and use the claimed methods. Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph be withdrawn.

35 U.S.C. § 112(b)

Claims 1-10 were rejected under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite.

While the Applicants do not agree with the rejections, solely in order to expedite prosecution, the Claims have been amended. The Applicants submit that the amendments to the claims submitted herewith render the indefiniteness rejections raised by the Office Action moot.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C. § 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite be withdrawn.

35 U.S.C. § 103

Claims 1-5 and 7-9 were rejected under 35 U.S.C. § 103 as being unpatentable over Garrett (WO 2009/108147 A1; 2009 – "Garrett") in view of Hani, et al. (WO 2010/105052 A1; 2010 – "Hani"). Claims 6 and 10 were rejected under 35 U.S.C. § 103 as being unpatentable over Garrett in view of Hani, et al., as applied above to claims 1-5 and 7-9, taken in further view of Garrett (WO 2009/061298; 2009). The Applicants submit that Claims 1-10 are not obvious in view of the cited references, at least for the reasons stated below. The Applicants note that the arguments presented below and the affidavit submitted herewith are substantially the same or the same as presented in the parent case (US 14/082,955), which claimed the formulation recited in the currently claimed method of use. The arguments and affidavit resulted in the allowance of the parent case.

First, Garrett teaches that a preferred composition comprises about 5% w/w dapsone wherein about 0.85% w/w carbopol 980 is used as a thickening agent.[1] The instant claims recite a new formulation of dapsone wherein the active ingredient is about 7.5% w/w dapsone and an entirely new thickening agent is employed. The new formulation of the instant claims does not include a carbomer such as Carbopol®, but instead utilizes as acrylamide/sodium acryloyldimethyl taurate copolymer, also known as "Sepineo™ P 600," and at a much higher concentration (about 2% to about 6% w/w) as compared to what Garrett teaches for its thickening agent.

Hani teaches a crosslinked PVP polymer for use in low pH topical formulations. While Hani may teach that acrylamide/sodium acryloyldimethyl taurate copolymer may be useful as ***an additional*** thickener with its PVP polymer, it certainly does not teach or suggest the use of Sepineo™ P 600 ***as the sole thickener*** in a topical dermatological formulation prepared with an active pharmaceutical ingredient. Moreover, the only mention of an acrylamide/sodium acryloyldimethyl taurate copolymer is found in paragraph [00118] of Hani, where it is included in a vast laundry list of other potential second thickeners. Finally, there is no guidance as to ***how much*** Sepineo™ P 600 one of ordinary skill in the art would use if it were to be selected from this laundry list in Hani.

Therefore, there are at least three significant distinctions between the present invention and the teachings of the cited art:

(i) The specific amount of dapsone recited in the instant claims; and

(ii) The use of Sepineo™ P 600 as the sole thickening agent in a topical dermatological formulation comprising dapsone; and

(iii) The specific amount of Sepineo™ P 600 recited in the instant claims.

The cited references do not teach or suggest these specific elements – alone or in combination. These facts, considered in view of the current law of obviousness, compels a finding of nonobviousness. The Applicants will now address the law cited by the Patent Office in the present Office Action as it applies to the present case.

[1] Garrett teaches other broader formulations of dapsone, but one skilled in the art seeking to improve upon the formulations of Garrett would look to its preferred embodiments.

The Office Action cites *KSR International Co. v. Teleflex Inc.* at page 6 of the Office Action for the proposition that a combination is obvious if it "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement…." 82 USPQ2d 1385, 1395-96 (U.S. 2007) (internal quotes omitted). This is true, but here we have new elements performing different functions not taught in the cited references, and the combination yields unexpected results. As discussed above, there are at least three new elements: the specific amount of dapsone, the use of Sepineo™ P 600 as the sole thickening agent, and the specific amount of Sepineo™ P 600. None of these elements are taught or suggested in either Garrett or Hani. The combination of these elements is neither taught nor suggested in either Garret or Hani. And as will be demonstrated below, the Applicants present unexpected results from this combination. For these reasons, the Patent Office's reliance on the above selection from *KSR* is inapplicable to the facts of this case.

Furthermore, the Patent Office's reliance on *Wertheim*, *Woodruff*, *Peterson* and *Harris* at page 7 of the Office Action is inapplicable to the presently amended claims as it relates to the specific amount of dapsone, as these cases clearly apply only to questions of the alleged obviousness of ***narrow ranges*** within broad ranges. And again, the specific selection of about 7.5% w/w dapsone is nonobvious based on the teachings of Garrett, which prefers a 5% w/w concentration.

For the above reasons, the instant claims are not *prima facie* obvious over Garrett and Hani. There is simply no teaching or suggestion whatsoever that would leave one of ordinary skill in the art to the precise combination of elements of the claimed dapsone/Sepineo™ P 600 compositions.

Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C. § 103 be withdrawn.

Unexpected Results

As stated above, the Examiner has failed to make a *prima facie* case of obviousness of the instant claims based upon the cited art. But even assuming for sake

of argument that the Examiner had made a proper *prima facie* case, the instant claims would still be patentable over the cited art because the Applicants have demonstrated unexpected results sufficient to overcome the hypothetical *prima facie* case. *See, e.g., In re Chupp*, 816 F.2d 643 (Fed. Cir. 1987) (finding of unexpected results based on superior properties in the context of the pharmaceutical arts).

Filed herewith is the Declaration of co-inventor Kevin S. Warner, Ph.D. ("Warner Declaration"). The present inventors unexpectedly discovered that Carbopol® 980, the thickening agent used in the Applicant's previous 5% dapsone formulation (and taught as preferred in the art cited by the Patent Office), resulted in undesirable polymer aggregates during formulation studies which lead to the present invention. *See* Warner Declaration, paragraphs 7-8. Sepineo™ P 600, on the other hand, performed surprisingly better and proved to be a more robust thickening agent. *Id.* This was an important discovery, as the use of Sepineo™ P 600 allowed for higher concentrations of DGME (*i.e.*, 30-40% w/w) which were found to be incompatible with Carbopol® 980. *Id.*

The inventors also discovered that Sepineo™ P 600 thickened formulations provided a smaller dapsone particle size distribution as compared directly to Carbopol® 980. *Id.* at 9. These particles were found to be stable over the course of 6 months under accelerated conditions. *Id.*

Sepineo™ P 600 was therefore selected as the gelling agent for the 7.5% w/w dapsone formulation of the instant claims. *Id.* at 10. The inventors made this selection based on the combination of the above factors which was entirely unexpected and could not have been predicted based on the previous 5% w/w dapsone formulation (with Carbopol® 980) or the references cited by the Patent Office. These unexpected results, which are commensurate in scope with the instant claims, further support the patentability of the claimed invention and warrant the withdrawal of the Examiner's obviousness rejection. The Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Obviousness-Type Double Patenting

U.S. Patent No. 9161926

Claims 1-10 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 9161926. The Applicants submit that this rejection is statutorily improper because of the present application's status as a divisional application of U.S. Patent No. 9161926, and thus must be withdrawn.

The Office Action acknowledges the present application's status as a divisional of U.S Patent Application No. 14/082,955, which eventually issued as U.S. Patent No. 9161926. *See* November 18, 2015 Non-Final Office Action at page 2, lines 5-8. 35 U.S.C. § 121 states in part that "[a] patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application." This is commonly known as the "safe harbor" provision, which prevents, for example, a parent application from being used for a grounds of rejection of a child divisional application. Thus, because the present application is a divisional of U.S. Patent No. 9161926, the double patenting rejection of the present application in view of U.S. Patent No. 9161926 is improper and should be withdrawn.

U.S. Patent No. 8586010

Claims 1-5 and 7-9 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8586010, or the provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani, et al. (WO 2010/105052 A1; 2010).

Claims 6 and 10 have been rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 8586010, or the provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-7 and 13-19 of U.S. Patent Application No. 14/063,841, each alternatively taken in view of Garrett (WO 2009/108147 A1; 2009) and Hani, et al.

(WO 2010/105052 A1; 2010) as applied above to claims 1-5 and 7-9, further in view of Garrett (WO 2009/061298; 2009).

The Applicants submit that an obviousness-type double patenting rejection over Claims 1-10 of the '010 patent is improper. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by or would have been obvious over, the reference claims. MPEP § 804. The Applicants submit that the pending Claims of the current application are patentably distinct from Claims 1-10 of the '010 patent, because the Claims of the present application recite several non-obvious elements not recited in Claim 1-10 of the '010 patent, as explained in detail above.

Thus, because the pending Claims in the present application are patentably distinct from Claim 1 of the '010 patent, an obviousness-type double patenting rejection would be improper and thus should not be made.

Applicant requests a Notice of Allowance. The Examiner is invited to call the undersigned attorney if any issues remain unresolved.

Please use Deposit Account 01-0885 for the payment of any extension of time fees, and/or the payment of any other fees due in connection with the present response.

Dated: February 18, 2016

Respectfully submitted,

/Laura L. Wine/

Laura L. Wine
Reg. No. 68681
Attorney for Applicant

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner *et al.*	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Leslie A Royds Draper
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

DECLARATION OF KEVIN S. WARNER, PH.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Kevin S. Warner, Ph.D., hereby declare:

1. I am a co-inventor in the above-captioned patent application.

2. I am an employee of the Applicant, Allergan, Inc. I have a Bachelor's of Science in chemistry from Brigham Young University and a Ph.D. from the University of Utah in Pharmaceutics and Pharmaceutical Chemistry. I have 12 years of experience conducting research in the areas of dermal and ophthalmic formulation development and leading project teams responsible for all CMC aspects of product development from phase 1 to phase 3 at Allergan, Inc.

3. I have read the above-captioned patent application and its pending claims as of the date of this Declaration. I have read the obviousness rejections made in the

Office Action dated December 1, 2014 and the publications cited by the patent examiner therein (International Patent Publication No. WO 2009/108147 A1, International Patent Publication No. WO 2010/105052 A1,US Patent Publication No. 2006/0204526, and the Lubrizol product description of Carbopol 980).

4. I am part of a team at Allergan responsible for developing a new formulation of Allergan's Aczone (dapsone) Gel, 5% product, wherein dapsone concentration is increased to 7.5% w/w from the 5% w/w level in Aczone 5% Gel. An object of this development project was to facilitate once daily dosing by increasing the concentration of dapsone, as compared to the current twice daily dosing regimen for Aczone 5% Gel.

5. During the course of development of the 7.5% w/w dapsone formulation, we looked to increase DGME concentration above the 25% level in Aczone 5% Gel in order to increase the saturation solubility of dapsone. Dapsone solubility increases with DGME concentration. This increase allows for a dissolved fraction of dapsone (dissolved fraction is calculated as the ratio of dapsone saturated solubility at 25 °C / dapsone concentration) comparable to that of Aczone 5% gel.

6. Under my supervision, a preliminary evaluation of thickeners suitable for use in the dapsone 7.5% gel formulation was performed. Five candidates were screened for their ability to thicken the proposed formulation: Carbopol® 980, Sepineo™ P 600, PPG-12/SMDI Copolymer (4,4'-Diisocyanatodicyclohexylmethane, polypropylene glycol polymer), Povidone/Eicosene (30:70), and Polyvinyl Alcohol. From this screening evaluation, we identified Carbopol 980 and Sepineo P 600 as promising gelling agents.

7. In additional experiments under my supervision, formulations containing Carbopol 980 showed undesired polymer aggregates at 40% diethylene glycol monoethyl ether ("DGME") concentration. This aggregation was not observed

with formulations containing Sepineo P 600 at 40% DGME. These results indicated that Sepineo P 600 is a more robust thickener and therefore more desirable for use in the gel formulation. I did not expect to observe Carbopol 980 incompatibility at a concentration of 40% DGME, especially because Carbopol 980 is compatible at concentrations of 25% DGME.

8. Based on the unexpected observation of Carbopol 980 incompatibility with 40% DGME, the thickener was changed from Carbopol 980 to Sepineo P 600 to mitigate the risk of polymer aggregation in DGME containing formulations.

9. In additional experiments under my supervision, a dapsone particle size assessment revealed that formulations thickened with Sepineo P 600 provided a smaller dapsone particle size as compared to Carbopol 980. The compositions of the formulations evaluated for particle size are outlined in Table 1 of Appendix A of this Declaration. Particle size data are provided in Table 2 (HORIBA data) of Appendix A of this Declaration. The data show that recrystallized dapsone particle size is smaller in the Sepineo P 600 formulation as compared to a Carbopol 980 formulation. I observed this difference even after 6 months storage under accelerated conditions (40 °C/75% RH) thereby showing no significant change in the particle size over time. This stability data suggests that particle size does not change over time irrespective of the stabilizer used (Carbopol or Sepineo). Thus a smaller initial particle size appears to be more relevant parameter that defines improved formulation characterization.

10. Based on the above results, my co-inventors and I selected Sepineo P 600 as the gelling agent for our dapsone 7.5% gel formulation. We made this selection due to Sepineo P 600's compatibility with concentrations of DGME greater than 25% and its improvement in dapsone particle size relative to Carbopol 980.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 2, 2015

Kevin S. Warner, Ph.D.

APPENDIX A

Table 1 Composition of Formulations Analyzed for Dapsone Particle Size Comparison in Sepineo P 600 vs. Carbopol 980

Component	% w/w		
	ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600	7.5% Dapsone, 25% DGME, 1% Carbopol	7.5% Dapsone, 30% DGME, 1% Carbopol
Dapsone	7.5	7.5	7.5
DGME	30	25	30
Carbopol 980	N/A	1	1
Sepineo P 600	4	N/A	N/A
Methylparaben	0.2	0.2	0.2
Triethanolamine	N/A	QS pH 5.5 – 6.5	QS pH 5.5 – 6.5
Purified Water	QS 100	QS 100	QS 100

N/A = Not Applicable

Table 2 Particle Size (HORIBA) Data Comparing Dapsone Particle Size in Sepineo P 600 vs. Carbopol 980 at Time = 0 and 6 Months at 40 °C/75% RH

Formulation Description	D90 (µm)	
	T=0	T=6 Months 40 °C/75% RH
ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600 (Lot ELE)	61	72
7.5% Dapsone 25% DGME 1% Carbopol (Lot ELF)	123	114
7.5% Dapsone 30% DGME 1% Carbopol (Lot ELG)	172	169

Electronic Acknowledgement Receipt

EFS ID:	24950420
Application Number:	14885805
International Application Number:	
Confirmation Number:	9004
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	19107 DIV (AP)
Receipt Date:	18-FEB-2016
Filing Date:	16-OCT-2015
Time Stamp:	14:15:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		19107DIV_Response_021816.pdf	4996802 7120d53891d5255b4f1da123122efdb7ee57dcbb	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	11
	Affidavit-traversing rejectns or objectns rule 132	12	16
Warnings:			
Information:			
	Total Files Size (in bytes):	4996802	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14885805
Filing Date	2015-10-16
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107-US-DIV-AP

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5863560		1999-01-26	David Osborne	
	2	6060085		2000-05-09	David Osborne	
	3	6620435		2003-09-16	David Osborne	
	4	7531694		2009-05-12	Villa, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060204526		2006-09-14	Lathrop et al	
	2	20100029781		2010-02-04	Jerome A. Morris	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14885805
	Filing Date	2015-10-16
	First Named Inventor	WARNER KEVIN S
	Art Unit	1629
	Examiner Name	Draper, Leslie A. Royds
	Attorney Docket Number	19107-US-DIV-AP

	3	20100130613		2010-05-27	DRENO	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-108147	WO		2009-09-03	QLT USA, INC.		☐
	2	WO2010105052	WO	A1	2010-09-16	ISP INVESTMENTS INC.		☐
	3	WO2011-014627	WO		2011-02-03	Allergan, Inc.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	DRAELOS, ZOE D. ET AL., Two Randomized Studies Demonstrate The Efficacy and Safety Of Dapsone Gel, 5% For The Treatment Of Acne Vulgaris, Journal Of American Academy Of Dermatology, 03/2007, 26 Pages, 56, US	☐
	2	Lubrizol (Online). "Viscosity of CARBOPOL Polymers in Aqueous Systems". (Retrieved 2014-03-18). Retrieved from the Internet:<URL:http://www.lubrizol.com/Life-Science/Documents/Pharmaceutical/Technical-Data-Sheets/TDS-730-Viscosity-Carbopol-in-Aqueous-Systems.pdf>.	☐
	3	Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, International Application No. PCT/US2013/070613, International Filing Date, November 18, 2013, Date of Mailing February 12, 2014	☐

If you wish to add additional non-patent literature document citation information please click the Add button

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14885805
	Filing Date	2015-10-16
	First Named Inventor	WARNER KEVIN S
	Art Unit	1629
	Examiner Name	Draper, Leslie A. Royds
	Attorney Docket Number	19107-US-DIV-AP

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14885805
Filing Date	2015-10-16
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107-US-DIV-AP

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Laura L. Wine/	Date (YYYY-MM-DD)	2016-02-18
Name/Print	Laura L. Wine	Registration Number	68681

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Banerjee, Krishna
ALLERGAN, INC.
2525 Dupont Drive
Irvine CA 92612
ETATS-UNIS D'AMERIQUE

DOCKETED BY
RESPONSE DUE 08-12-14
ACTION Amd. 19 Amd / IDS To Atty

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 19107PCTAP	Date of mailing *(day/month/year)* 12 February 2014 (12-02-2014)
International application No. PCT/US2013/070613	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant ALLERGAN, INC.	International filing date *(day/month/year)* 18 November 2013 (18-11-2013)

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	HOHMANN, Birgit Tel: +49 (0)89 2399-8798

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
19107PCTAP		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2013/070613	18 November 2013 (18-11-2013)	20 November 2012 (20-11-2012)
Applicant		
ALLERGAN, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/070613

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/10 A61K31/136 A61K31/192
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/014627 A1 (ALLERGAN INC [US]; AHLUWALIA GURPREET [US]; WARNER KEVIN S [US]; CHEN) 3 February 2011 (2011-02-03) page 3, line 10 - page 7, line 32; claims 1-20; figures 1-5; examples 1-11; tables 1, 2A, 2B	1-20
X	WO 2009/108147 A1 (QLT USA INC [US]; GARRETT JOHN STEVEN [US]) 3 September 2009 (2009-09-03) page 12, line 1 - page 13, line 11 page 13, line 30 - page 14, line 8 page 13, line 28 - page 17, line 26 page 19, line 21 - page 2015 page 24, lines 18-24 page 21, line 30 - page 23, line 22	1-20

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2014	12/02/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Toulacis, C

Form PCT/ISA/210 (second sheet) (April 2005)

International application No
PCT/US2013/070613

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/029781 A1 (MORRIS JEROME A [US]) 4 February 2010 (2010-02-04) paragraphs [0014], [0030], [0032], [0057], [0070], [0078] -----	1-20
A	FOR THE UNITED STATES/CANADA DAPSONE GEL STUDY GROUP DRAELOS ET AL: "Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, C.V. MOSBY, ST. LOUIS, MO, US, vol. 56, no. 3, 20 February 2007 (2007-02-20), pages 439.e1-439.e10, XP005893393, ISSN: 0190-9622, DOI: 10.1016/J.JAAD.2006.10.005 the whole document -----	1-20

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/070613

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011014627 A1	03-02-2011	AU 2010278915 A1	01-03-2012
		CA 2769640 A1	03-02-2011
		EP 2459172 A1	06-06-2012
		JP 2013500984 A	10-01-2013
		RU 2012104572 A	10-09-2013
		WO 2011014627 A1	03-02-2011
WO 2009108147 A1	03-09-2009	AU 2008351422 A1	03-09-2009
		CA 2714674 A1	03-09-2009
		EP 2249765 A1	17-11-2010
		JP 2011513304 A	28-04-2011
		US 2010310480 A1	09-12-2010
		WO 2009108147 A1	03-09-2009
US 2010029781 A1	04-02-2010	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2013/070613	18.11.2013	20.11.2012

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K47/10 A61K31/136 A61K31/192

Applicant
ALLERGAN, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Toulacis, C Telephone No. +49 89 2399-8638

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1-7, 9-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claims 18 to 20 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Their assessment will be carried out based on the alleged effects of the composition searched in the International Search Report.

Reference is made to the following documents:

D1 = WO 2011/014627 A1 (ALLERGAN INC [US]; AHLUWALIA GURPREET [US]; WARNER KEVIN S [US]; CHEN) 3 February 2011 (2011-02-03)

D2 = WO 2009/108147 A1 (QLT USA INC [US]; GARRETT JOHN STEVEN [US]) 3 September 2009 (2009-09-03)

D3 = US 2010/029781 A1 (MORRIS JEROME A [US]) 4 February 2010 (2010-02-04)

Claims 1-7, 9-20

(N)

A composition comprising dapsone at a concentration of 0.5-10%, diethylene glycol monoethyl ether at a concentration of 1-50% , Carbomer 980® at a concentration of 0.05-1.5 %, NaOH, triethanolamine, Ethanol, Methylparaben and EDTA disodium, is already disclosed in document D1 (see page 8, Table 1 and pages 9-11, Tables 2A, 2B).

Document D1, also discloses the use of said compositions in the treatment of dermatological conditions as defined in present claims 18-20 (see D1; page 3, lines 16-23).

Similarly document D2 discloses a pharmaceutical composition comprising 5% dapsone, 0.85% Carbomer 980, 25% diethylene glycol monoethyl ether (DGME), 0.2% methylparaben, 0.2% sodium hydroxide, and 68.75% purified water. The composition additionally comprises a thickening agent, a high-boiling, nonionic organic

solvent, a preservative, a base agent, an antioxidant, a fragrance, a colorant, and/or a sunscreen. The dapsone is present at 0.5-10% (See D2; page 12, line 1 - page 13, line 11; page 13, line 30 - page 14, line 8; page 13, line 28 - page 17, line 26; page 19, line 21 - page 2015; page 24, lines 18-24; page 21, line 30 - page 23, line 22).

Furthermore, document D3 discloses a topical gel formulation, comprising about 0.5% to 4.0% Carbomer, about 66.95% water; about 25% diethylene glycol monoethyl ether (i.e., ethoxydiglycol); about 0.2% methylparaben; about 5% dapsone; and about 0.2% sodium hydroxide (see D3; [0069], [0070]).

Said disclosures fall within the scope of present claims 1-7 and 9-20.

(IS)

Although no final decision can be made in respect of inventive step until the requirements of novelty have been satisfied, it appears that the problem which faced the skilled person at the priority date of the present Application has already been described and solved in documents D1-D3 (see particularly D1; page 7, lines 19-21).

(IA)

The industrial applicability of claims 1-7 and 9-17 is given.

Claim 8

(N)

The subject-mater of claim 8 is novel over the documents cited in the search report, due to the defined second solubilizing agent being propylene carbonate.

(IS)

However, propylene carbonate is considered to be a possibility among the solubilising agents from which the person skilled in the art would select, in accordance with circumstances, without the exercise of inventive skill in order to solve the problem posed.

Moreover, there is no indication or any data in the description of the present application, which suggest that the claimed compositions show any unexpected effect or property, due to the second solubilizing agent being propylene carbonate.

(IA) The industrial applicability is beyond any doubt.

XS CPRTENFRDE

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Published:

.... *with international search report (Art. 21(3))*

(54) Title: DAPSONE TO TREAT ROSACEA

(57) Abstract: The methods described herein provide treatment of rosacea using topical formulations of dapsone. The methods also provide treatment of rosacea with topical dapsone in combination with other active agents, including metronidazole. The methods avoid negative hematologic side effects, including hemolysis and hemolytic anemia, that are associated with oral administration of dapsone.

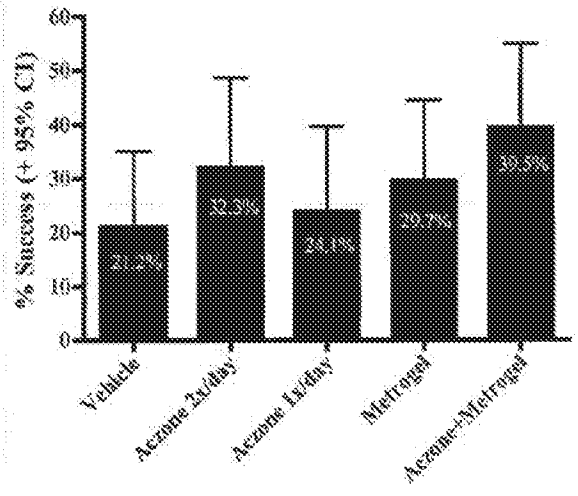

FIG. 11

WO 2009/108147 A1

DAPSONE TO TREAT ROSACEA

Background of the Invention

Rosacea is a dermatological syndrome affecting approximately 14 million Americans. It is characterized by flushing of the skin, erythema, inflammatory papules and pustules, edema, telangiectasia, ocular symptoms and rhinophyma. To date, the etiology of rosacea is unknown and there is no clearly recognized cure (Bikowski and Goldman, 2004; Stone and Chodosh, 2004).

Four subtypes and one variation of rosacea have been defined. The subtypes are papulopustular rosacea, erythematotelangiectatic rosacea, phymatous rosacea, and ocular rosacea; the rosacea variation is granulomatous rosacea. Some patients may have features of more than one subtype simultaneously, and differences in severity occur within each subtype.

Management of rosacea is difficult because of the complexity of the syndrome and the sensitivity of rosacea-affected skin. Various therapies, including topical application of metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline, are used in the management of rosacea with varying rates of success. Systemic therapy with oral tetracyclines, metronidazole and isotretinoin is also employed in the management of rosacea (Buechner, 2005). Dapsone antibiotic is effective for treating rosacea redness, facial flushing, papules and pustules when administered orally; however, the side effect profile makes the risk/benefit ratio too high for most rosacea sufferers (Nase, 2005).

What is needed are safe, effective treatments for the management of rosacea symptoms.

Summary of the Invention

The invention is directed to the treatment of rosacea. The invention includes a method to treat rosacea by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier to a patient. In preferred embodiments, the rosacea is papulopustular rosacea. In other embodiments, the rosacea is ocular rosacea. The invention is also directed to the

treatment of ocular disorders. The invention includes a method to treat an ocular disease or disorder by topically administering a pharmaceutical composition of dapsone and a pharmaceutically acceptable carrier.

In some embodiments, the dapsone of the topical composition is entirely dissolved in the carrier; or partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid. In an entirely dissolved state, dapsone exists completely in solution in the solvent, with no solid dapsone present. If the dapsone is partially dissolved and partially microparticulate, a portion of the dapsone is present in solution and a portion of the dapsone is present in a solid form. A dapsone emulsion includes two immiscible, unblendable substances wherein one substance (the dispersed phase) is dispersed in the other (continuous phase). The dapsone can be part of the dispersed phase or part of the continuous phase of the emulsion. A dapsone suspension is a heterogenous fluid containing solid particles of dapsone dispersed throughout a fluid. A dapsone colloid is a homogenous mixture of dispersed dapsone particles that are distributed evenly and stably throughout the continuous phase.

In certain embodiments, the pharmaceutical composition is a lotion, gel, ointment, cream, emulsion, suspension, spray, or cleanser. In a preferred embodiment, the pharmaceutical composition is a semisolid aqueous gel. The semisolid aqueous gel includes a thickening agent, water, a solvent, preservative, microparticulate dapsone, dissolved dapsone, and caustic material. In a preferred embodiment, the caustic material is a base agent. In a preferred embodiment, the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum of the epidermis and be absorbed into the lower two-thirds of the pilosebaceous unit; and microparticulate dapsone that is retained in or above the stratum corneum to serve as a reservoir or to provide dapsone to the supracorneum zone, crossing the stratum corneum of the epidermis only minimally as a solid. The solid microparticulate dapsone reservoir is slowly dissolved in body fluids before it is delivered through the stratum corneum. In preferred embodiments, the dapsone makes up about 0.5% to 10% of the pharmaceutical composition. The microparticulate dapsone can be a crystalline precipitate or an amorphous precipitate. Antioxidants, fragrance, colorants, sunscreens, or combinations thereof may also be present in the topical composition. In preferred

embodiments, the dapsone composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

The methods described herein include the treatment of papulopustular rosacea by applying the dapsone composition once or twice daily. In preferred methods the dapsone composition is applied twice daily. The methods additionally include the use of the dapsone pharmaceutical composition alone or in combination with other pharmaceutical compositions for rosacea, including topical and systemic treatments. The treatments are administered simultaneously or sequentially and include oral metronidazole, isotretinoin, tetracyclines including doxycycline, and topical metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline. In some embodiments, the dapsone and other pharmaceutical are present in the same composition. In other embodiments, the dapsone and other pharmaceutical are present in separate compositions. In preferred embodiments, the dapsone pharmaceutical composition is applied topically in the AM and a separate metronidazole composition is applied topically in the PM, or vice versa.

In some embodiments, the patient has mild to severe papulopustular rosacea. In some embodiments, the patient has mild to moderate papulopustular rosacea. In other embodiments, the patient has moderate to severe papulopustular rosacea. In preferred embodiments, the rosacea is moderate to severe papulopustular rosacea. In some embodiments, the patient has at least ten papulopustular lesions before treatment, or preferably at least twenty papulopustular lesions before treatment. In a preferred embodiment, the number of papulopustular rosacea lesions is reduced by administering the dapsone composition topically. In some embodiments, the methods described herein result in blood plasma levels of dapsone of less than about 100 ng/mL.

In some embodiments, the patient has an Investigator's Global Assessment score of 3 or higher before treatment. In some embodiments, treatment results in a mean reduction of at least 13 papulopustular lesions. In some embodiments, treatment results in a mean reduction of at least 43 % of the papulopustular lesions.

Brief Description of the Figures

Figure 1 shows the mean change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line.

Figure 2 shows the mean percent change from baseline in inflammatory lesion counts in the ITT population having ≥ 10 lesions (ITT).

Figure 3 shows mean change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 4 shows mean percent change from baseline in inflammatory lesion counts for subjects with <20 lesions.

Figure 5 shows the mean change from baseline in lesion counts for the subgroup of subjects with ≥ 20 lesions.

Figure 6 shows mean percent change from baseline in inflammatory lesion counts for subjects with ≥ 20 lesions.

Figure 7 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 8 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 in the intent to treat (ITT) population having ≥ 10 inflammatory lesions.

Figure 9 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with <20 inflammatory lesions.

Figure 10 shows the Investigator's Global Assessment (IGA) success rate over the course of the study in subjects with ≥ 20 lesions.

Figure 11 summarizes the Investigator's Global Assessment (IGA) success rate at week 12 for the subgroup of subjects with ≥ 20 lesions.

Detailed Description of the Invention

Definitions

As used herein, "adverse event" means any adverse change in health or "side-effect" that occurs in a patient who is participating in a study while the patient is receiving treatment (dermatological composition or vehicle) or within a pre-specified period of time after their treatment has been completed.

As used herein, the term "colloid" refers to a homogenous mixture of two separate phases. The dispersed phase is made of tiny particles or droplets that are distributed evenly throughout the continuous phase. Colloids are stable mixtures and the dispersed phase generally does not settle out of the mixture.

As used herein, "dapsone" refers to the chemical compound dapsone having the chemical formula $C_{12}H_{12}N_2O_2S$ as well as bis(4-aminophenyl)sulfone, 4',4'-diaminodiphenyl sulfone and its hydrates, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, diaphenylsulfone, dapsone analogs, and dapsone related compounds. "Dapsone analogs" refers to chemical compounds that have similar chemical structures and thus similar therapeutic potential to dapsone such as the substituted bis(4-aminophenyl)-sulfones. "Dapsone related compounds" refers to chemical compounds that have similar therapeutic potential, but are not as closely related by chemical structure to dapsone such as the substituted 2,4-diamino-5-benzylpyrimidines.

As used herein, the term "emulsion" describes a mixture of two immiscible, unblendable substances. The dispersed phase is dispersed in the continuous phase. For example, oil and water will form an emulsion when mixed together. In the compositions described herein, the oil phase may include but is not limited to fatty alcohols, acids, or esters such as cetyl palmitate, cetyl alcohol, stearyl alcohol, stearic acid, isopropyl stearate, glycerol stearate, mineral oil, white petrolatum, or other oils alone or in combination. Surfactants may be present in the emulsion to increase kinetic stability. Suitable emulsifiers that may be added to the compositions described herein include, but are not limited to, steareth 20, ceteth 20, sorbitan sesquioleate, sorbitan mono-oleate, propylene glycol stearate, dosium lauroyl sarcosinate, polysorbate 60, or combinations.

As used herein, "gel" refers to a colloid in a more solid form than a solution. A gel is also a jelly-like material formed by the coagulation of a colloidal liquid. Many gels have a fibrous matrix and fluid filled interstices. Gels are viscoelastic rather than simply viscous and can resist some mechanical stress without deformation.

As used herein, the term "mild rosacea" refers to papulopustular rosacea that includes mild erythema and several small papules/pustules.

As used herein, the term "moderate rosacea" refers to papulopustular rosacea that includes moderate erythema, with several small or large papules/pustules, and up to two nodules.

As used herein, the term "severe rosacea" refers to papulopustular rosacea that includes severe erythema and numerous small and/or large papules/pustules, and up to several nodules.

As used herein, the term "microparticulate" refers to any solid form of an active agent (dapsone) that is not dissolved in the topical composition. The microparticulate described herein may be in the form of flakes or crystals, and includes a precipitate of dapsone that results from the addition of water and the solvent or mixed solvent system. The microparticulate may comprise a crystalline precipitate or an amorphous precipitate.

As used herein, the term "ointment" means a semisolid, oil-based topical formulation. Examples of ointments include essentially non-aqueous mixtures of petrolatum, lanolin, polyethylene glycol, plant or animal oils, either hydrogenated or otherwise chemically modified. An ointment may also contain a solvent in which an active agent is either fully or partially dissolved.

As used herein, "pharmaceutically acceptable carrier" refers to a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering an active agent to a patient. Pharmaceutically acceptable carriers are nontoxic to the cell or patient being exposed thereto at the dosages and concentrations employed. Often, the physiologically acceptable carrier is an aqueous pH buffered solution. Pharmaceutically acceptable carriers are readily available to the public. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Pharmaceutically acceptable carriers may include antiadherents, binders, coatings, disintegrants, fillers, diluents, colorants, glidants, lubricants, and preservatives. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives. In a preferred embodiment, the pharmaceutically acceptable carrier includes ethoxydiglycol, also known as diethylene glycol monoethyl ether (DGME).

As used herein, the term "suspension" refers to a heterogenous fluid containing solid particles dispersed throughout. The suspended phase or suspensoid is dispersed throughout the liquid in a moderately finely divided state, but not so finely divided as to acquire the stability of a colloidal system. The suspended phase will eventually settle out of the suspension.

The term "topical" or "topical surface" as used herein refers to the route of administration of a composition that involves direct application to the surface of the body being treated. Topical application may be to the skin, or to a mucous membrane, also called mucosa, lining all body passages that communicate with the exterior such as the respiratory, genitourinary, and alimentary tracts, and having cells and associated glands that secrete mucous. Topical application may be to mucous membranes of nose, mouth, eye, eyelid inner surface, etc., or may be to the surface of intact or compromised skin. Examples of topical application include application of gels or other semisolids to rub-on, solutions to spray, or liquids to be applied by an applicator, for example, as eye drops. Rinse-off application with washes, cleansers, or shampoos are also examples of topical application. Areas of the body especially suitable for application of the composition described herein include sites where rosacea symptoms may be present, including the skin of the face, scalp, ears and neck, and the eyes.

As used herein, the term "treat", "treatment", or "treating" refers to the reduction in number and/or severity of individual rosacea lesions, prevention of the development of rosacea symptoms including papulopustular lesions, or global improvement in the appearance of rosacea. Success of treatment may be indicated by a reduction from baseline in the raw number of papulopustular inflammatory lesions, by a percent reduction from baseline in papulopustular inflammatory lesions, or by an improvement from baseline in an Investigator's Global Assessment (IGA) score.

Methods of Treatment

The method of the invention described herein treats rosacea conditions, e.g., papulopustular, erythematotelangiectatic, phymatous, and ocular rosacea, by the topical application of a composition comprising dapsone and a pharmaceutically acceptable carrier. The composition is applied as needed to relieve rosacea symptoms. In some embodiments, the composition is applied

every other day. In some embodiments, the composition is applied once daily. In some embodiments, the composition is applied twice daily. In certain embodiments, the composition is applied for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, at least eight weeks, at least nine weeks, at least ten weeks, at least eleven weeks, or at least twelve weeks. In some preferred embodiments, the composition is applied for at least twelve weeks. In other preferred embodiments, the composition is applied for at least six months, at least nine months, or at least a year.

Rosacea

Rosacea is a multifactorial chronic disorder that most often affects the skin of the central face including the nose, forehead, cheeks, and chin. Rosacea usually affects fair-skinned people 30 to 50 years of age who tend to blush or flush easily. Four subtypes of rosacea are described: papulopustular, erythematotelangiectatic, phymatous, and ocular (Wilkin et al. 2002; Bikowski and Goldman, 2004). Granulomatous rosacea is considered to be a part of the spectrum of rosacea, but is referred to as a variant, rather than a subtype, of rosacea (Khokhar and Khachemoune 2004).

Papulopustular rosacea is characterized by persistent central facial erythema with transient, central facial papules, pustules or lesions of both types. In preferred embodiments, mild to severe papulopustular rosacea is treated. In a more preferred embodiment, moderate to severe papulopustular rosacea is treated. Erythematotelangiectatic rosacea is characterized by flushing and persistent central facial erythema, with or without telangiectasia. Phymatous rosacea is characterized by thickening skin, irregular surface nodularities, and enlargement, which may occur on the nose, chin, forehead, cheeks or ears. Ocular rosacea is characterized by a foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema. Granulomatous rosacea is characterized by noninflammatory, hard, brown, yellow or red cutaneous papules; or nodules of uniform size (Bikowski and Goldman, 2004).

In a recent study of clinical patterns of rosacea, papules and pustules were found in 83% and 67% of a sample of 108 rosacea patients, respectively

(Sibenge and Gawkrodger, 1992). In the papulopustular subtype of rosacea, patients typically present with persistent central facial erythema with transient papules or pustules or both. Symptoms of burning, stinging, and dry skin are common (Wilkin et al. 2002; Dahl 2004). Other symptoms include flushing, erythema, and telangiectasia. While the exact pathogenesis of rosacea is unknown, inflammatory and vascular components are believed to be important in its pathogenesis.

The methods of the invention described herein include treatment of papulopustular rosacea lesions. In certain embodiments, the treatment of rosacea lesions results in a decrease or reduction from the baseline number of lesions by at least 2 lesions, at least 3 lesions, at least 4 lesions, at least 5 lesions, at least 6 lesions, at least 7 lesions, at least 8 lesions, at least 9 lesions, at least 10 lesions, at least 11 lesions, at least 12 lesions, at least 13 lesions, at least 14 lesions, at least 15 lesions, at least 16 lesions, at least 17 lesions, at least 18 lesions, at least 19 lesions, at least 20 lesions, at least 30 lesions, at least 40 lesions, or more than 40 lesions. In certain embodiments, the treatment of rosacea lesions results in a percentage decrease or reduction of lesions from baseline of at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, or more than 75%.

About half of all rosacea sufferers also have some involvement of the eyes, known as ocular rosacea (Starr and McDonald, 1969). Eye problems may precede the common skin-related rosacea symptoms though it more common for the skin symptoms to appear first (Borrie, 1953). Ocular rosacea symptoms include dry eyes or tearing, redness, burning, pain, a gritty feeling in the eye, scales and crusts on the eyelids, sensitivity to light and blurry vision (Jenkins 1979).

Blepharitis, which includes inflammation of eyelashes or lid margins, is commonly seen in ocular rosacea. Blepharitis often results in red, itchy, burning eyes and lashes as well as scales and crusts on the eyelids. Sties, which are infections of eyelash follicles, may be present. Ocular rosacea sufferers may also have chalazia or meibomitis, characterized by enlarged, inflamed or plugged meibomian glands (which normally lubricate the eyelids). Scleritis and episcleritis, which are inflammatory conditions of the white outer coating of the

eye (sclera) and connective tissue between the conjunctiva and sclera (episclera) may also be present in ocular rosacea.

Keratitis and iritis, which are infections or inflammation of the cornea and iris, respectively, may also be present in patients with ocular rosacea. These conditions may result in severe eye pain, blurry vision, formation of pus, and sensitivity to light. In severe ocular rosacea, ulcers may be present at the border of the cornea and sclera. This corneal ulceration, if untreated, may lead to perforation of the eye, a potentially blinding complication.

Management of rosacea is difficult because of the complexity of the syndrome and the sensitivity of rosacea-affected skin. Various therapies, including topical application of metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline, are used in the management of rosacea with varying rates of success. Systemic therapy with oral tetracyclines, metronidazole and isotretinoin is also employed in the management of rosacea (Buechner, 2005). Oral dapsone antibiotic is effective for treating rosacea redness, facial flushing, papules and pustules; however, the side effect profile makes the risk/benefit ratio too high for most rosacea sufferers (Nase, 2005).

Ocular Indications

In addition to ocular rosacea, other ocular diseases may be treated with the topical dapsone compositions of the present invention. These diseases may be associated with inflammation, infection or other pathologies and the ocular involvement may be a primary or secondary manifestation of the disease or disorder. These diseases and disorders include conjunctivitis; scleritis including nodular scleritis secondary to Sweet's syndrome; vasculitis including autoimmune vasculitis and retinal vasculitis of Eales' disease; uveitis including granulomatous uveitis and panuveitis; ocular cicatrical pemphigoid; ocular leprosy; ocular manifestations of arachnid evenomation, Behçet disease, linear IgA disease, relapsing polychondritis, peripheral keratitis, tuberculosis, Hodgkin lymphoma, non-Hodgkin lymphoma, T-cell lymphoma and Reiter's syndrome; tumors of the eyelids; erythema elevatum diutinum; eyelid manifestations of erosive lichen planus; and pneumocystis carinii choroiditis associated with AIDS. The topical dapsone compositions of the present invention may be particularly formulated for treatment of ocular conditions. These formulations

will be known to those of skill in the art and include drops, gels, ointments, cleansers and other topical formulations.

Dapsone

Dapsone was first synthesized in 1908 and has been used medically as an antibiotic and an anti-inflammatory. Dapsone is a bis(4-aminophenyl)sulfone also known as 4',4'-diaminodiphenyl sulfone, 4,4'-sulfonylbisbenzeneamine, 4,4'-sulfonyldianiline, and diaphenylsulfone. Dapsone has been used orally for the treatment of acne (Ross, 1961).

Dapsone analogs and related compounds have been described in U.S. Pat. Nos. 4,829,058 and 4,912,112 to Seydel et al. The '058 patent discloses substituted bis(4-aminophenyl)sulfones useful for inhibiting growth of bacteria, mycobacteria, and plasmodia. Some of these compounds were also tested against dapsone for toxicity and anti-inflammatory activity. In the '112 patent, substituted 2,4-diamino-5-benzyl pyrimidines having antimicrobial activity particularly against mycobacteria are described. Some of these compounds were also tested against dapsone for toxicity (Coleman et al., 1996) and anti-inflammatory activity (Coleman et al., 1997). The teachings of these references in combination with subsequent publications showed that these analogs and related compounds have activity similar to dapsone and would be expected to have similar treatment efficacy.

Currently, use of oral dapsone is generally limited, as its use may be associated with hematologic side effects, including hemolysis and hemolytic anemia that are dose-dependent and occur more frequently with increasing dose (Zhu and Stiller 2001; Jollow et al., 1995). The mechanism of dapsone-related hemolysis and hemolytic anemia involves oxidative damage to red blood cells and is associated with the dapsone hydroxylamine metabolite (Prendiville et al., 1988).

Topical Dapsone Compositions

Topical dapsone formulations have been described in U.S. Pat. No. 5,733,572 to Unger et al., and U.S. Pat. Nos. 6,056,954; 6,056,955; 6,254,866; 6,248,324; and 6,277,399 to Fischetti et al. A topical composition including dapsone for acne treatment has been described in U.S. Pat. Nos. 5,863,560 and 6,060,085 to Osborne which are herein incorporated by reference in their entirety.

The topical compositions described herein include dapsone and a pharmaceutically acceptable carrier. The carriers described herein are media useful for topical delivery of dapsone and optionally any additional active agents. These media, which are preferably organic or organic/aqueous mixtures, may be formulated as eye drops, lotions, gels, ointments, creams, sprays, washes, cleansers, shampoos, roll-on or stick products, micro-emulsions, shake powders, aerosolized sprays or mousse, and bath additives. Additional pharmaceutical carriers will be known to those skilled in the art and this list should not be considered to be limiting.

The dapsone of the topical composition may be entirely dissolved in the carrier; partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid. In an entirely dissolved state, dapsone exists completely in solution in the solvent, with no solid dapsone present. If the dapsone is partially dissolved and partially microparticulate, a portion of the dapsone is present in solution and a portion of the dapsone is present in a solid form. A dapsone emulsion includes two immiscible, unblendable substances wherein one substance (the dispersed phase) is dispersed in the other (continuous phase). The dapsone can be part of the dispersed phase or part of the continuous phase of the emulsion. A dapsone suspension is a heterogenous fluid containing solid particles of dapsone dispersed throughout a fluid. A dapsone colloid is a homogenous mixture of dispersed dapsone particles that are distributed evenly and stably throughout the continuous phase.

Pharmaceutical carriers are pharmaceutically acceptable media for delivering active agent(s) to a patient. Pharmaceutically acceptable carriers include solvents, suspending agents or other vehicles that are nontoxic to the patient being exposed thereto at the dosages and concentrations employed. Pharmaceutical carriers of the compositions described herein will solubilize dapsone and any additional active agent(s) in whole or in part. Excipients present in the pharmaceutically acceptable carrier may include antiadherents, binders, coatings, disintegrants, fillers, diluents, colorants, glidants, lubricants, and preservatives.

In some embodiments, the topical compositions include a pharmaceutical carrier, dapsone, and an additional active pharmaceutical agent or agents. As described above, these dual agent compositions may be formulated as lotions,

gels, ointments, creams, sprays, washes, cleansers, shampoos, roll-on or stick products, micro-emulsions, shake powders, aerosolized sprays or mousse, and bath additives. The dapsone and additional active pharmaceutical agent(s) of the topical composition may be entirely dissolved; partially dissolved and partially microparticulate; or may be present as an emulsion, suspension or colloid as described above. Suitable additional active pharmaceutical agents are disclosed, e.g., in Physician's Desk Reference (PDR), Medical Economics Company (Montvale, NJ), (53rd Ed.), 1999; Mayo Medical Center Formulary, Unabridged Version, Mayo Clinic (Rochester, MN), January 1998; Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, (11th Ed.), Merck & Co., Inc. (Rahway, NJ), 1989; and references cited therein.

Additional active pharmaceutical agents include, but are not limited to, anti-inflammatory agents, keratolytics, anti-infectives and acidic compounds. Anti-inflammatory agents, including corticosteroids, relieve inflammation including swelling, itching, and redness of the skin. Keratolytics are agents that soften skin cells and ease the flaking and peeling process. Examples include salicylic acid and urea. Anti-infectives including antibiotics, antifungals and antiseptics combat bacteria, fungi, and parasites. Acidic compounds contain an organic acid group or are at least weakly acidic in an aqueous-based solution and include retinoic acid, azelaic acid and lactic acid. In preferred embodiments, the additional active pharmaceutical agent is metronidazole anti-infective.

In preferred embodiments, the topical compositions described herein include thickening agents or thickeners. These substances increase viscosity, stability and improve suspending capability when added to a mixture. Known thickeners include inorganic water thickeners, polymeric thickeners, additives that promote thickening via lamellar structuring of surfactants, organic crystalline thickeners, and mixtures thereof. Suitable polymer thickeners for use in the topical compositions include cationic thickeners, non-ionic thickeners and anionic thickeners. Useful thickeners are described in detail below.

In preferred embodiments, the topical compositions described herein include solvent systems comprising organic solvents. These carbon-containing liquids dissolve solids, liquids, or gaseous solutes to form a solution. Solvents are grouped into polar (hydrophilic) and non-polar (lipophilic) types. Useful solvents are described in detail below. In preferred embodiments, the solvent of

the topical compositions is diethylene glycol monoethyl ether (DGME), also known as ethoxydiglycol. In preferred embodiments, the topical composition of dapsone is formulated as an eye-drop and the solvent of such eye-drop compositions comprises a non-irritating solvent, more preferably diethylene glycol monoethyl ether (DGME), even more preferably DGME sold under the trade name "Transcutol™", even more preferably DGME having a percent purity of greater than 99.5%, such as those sold under the name "Transcutol™ CG," "Transcutol™ P" and "Transcutol™ HP."

Preservatives, antioxidants, fragrances, colorants, sunscreens, thickeners, suspending agents, enhancers, binders, disintegrants, fillers, diluents, colorants, glidants, lubricants, and other additives required to achieve pharmaceutically or cosmetically acceptable properties of the topical compositions may also be included. Topical compositions are not limited to these components, since one skilled in the art will be aware of additional components useful in the formulation of topical compositions.

The present compositions can include an alkali, also known as a base agent or caustic agent. The amount of alkali can be adjusted to change pH values of the topical compositions. The pH adjustment of the compositions of the present invention can be carried out by means of inorganic bases such as sodium hydroxide and potassium hydroxide; and organic bases such as triethylamine, diisopropanolamine, and triethanolamine (trolamine). The compositions may have a pH of about 7, e.g. 7.2, or below about 7. In other embodiments, the compositions of the present invention can be adjusted to have a pH below about 6.0, more specifically below about 5.5, even more specifically between about 4.0 to about 5.5, even more specifically between about 4.2 to about 5.4, or 4.4 to about 5.2, or about 4.8 ± 0.5.

Thickeners

Suitable thickeners for use in the topical compositions include non-ionic thickeners, cationic thickeners and anionic thickeners. Suitable non-ionic thickening agents include polyacrylamide polymers, crosslinked poly(N-vinylpyrrolidones), polysaccharides, natural or synthetic gums, polyvinylpyrrolidone and polyvinylalcohol. Specific examples of non-ionic thickening agents include methyl hydroxypropyl cellulose, xanthan gum, polysaccharide gum, hydroxyl propyl cellulose, hydroxyl propyl methyl

cellulose, hydroxyl ethyl cellulose, polyalkylene gylcols, and mixtures thereof. Suitable anionic thickening agents include acrylic acid/ethyl acrylate copolymers, carboxyvinyl polymers and crosslinked copolymers of alkyl vinyl ethers and maleic anhydride.

Polymer thickeners that may be used include those known to one skilled in the art, such as hydrophilic and hydroalcoholic gelling agents frequently used in the cosmetic and pharmaceutical industries. Preferably, the hydrophilic or hydroalcoholic gelling agent comprises "CARBOPOL®" (B.F. Goodrich, Cleveland, Ohio), "HYPAN®" (Kingston Technologies, Dayton, N.J.), "NATROSOL®" (Aqualon, Wilmington, Del.), "KLUCEL®" (Aqualon, Wilmington, Del.), or "STABILEZE®" (ISP Technologies, Wayne, N.J.). Preferably, the gelling agent comprises between about 0.2% to about 4% by weight of the composition. More particularly, the preferred compositional weight percent range for "CARBOPOL®" is between about 0.5% to about 2%, while the preferred weight percent range for "NATROSOL®" and "KLUCEL®" is between about 0.5% to about 4%. The preferred compositional weight percent range for both "HYPAN®" and "STABILEZE®" is between about 0.5% to about 4%.

"CARBOPOL®" is one of numerous cross-linked acrylic acid polymers that are given the general adopted name carbomer. These polymers dissolve in water and form a clear or slightly hazy gel upon neutralization with a caustic material such as sodium hydroxide, potassium hydroxide, triethanolamine, or other amine bases. "KLUCEL®" is a cellulose polymer that is dispersed in water and forms a uniform gel upon complete hydration. Other preferred gelling polymers include hydroxyethylcellulose, cellulose gum, MVE/MA decadiene crosspolymer, PVM/MA copolymer, or a combination thereof.

Solvents

In some embodiments, the topical compositions described herein are fluid solvent or mixed-solvent systems. The solvent can be an organic solvent, for example the solvent can include diethyleneglycol monoethyl ether (DGME), N-methylpyrrolidone (NMP), N,N-dimethylformamide, N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or any other substantially non-toxic solvent suitable for application to human skin, wherein the solvent has at least some water solubility. Combinations of any of these solvents can also be used. Additional examples of solvents include ethanol, propylene glycol, glycerol,

diethyleneglycol, triethyleneglycol, polyethylene glycol, propylene carbonate, pyrrolidone, *N*-methyl pyrrolidone, dimethylsulfoxide, triethanolamine, 1,4-butanediol, ethyl acetate, triacetin, diacetin, dimethyl isosorbide, and the like, alone or in combination.

Other solvents can be used in conjunction with water to form the liquid of the inventive method. These solvents include, but are not limited to: benzyl alcohol, denatured alcohol, methanol, isopropyl alcohol, propanol, acetone, chlorobutanol, methyl ethyl ketone, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, butyl alcohol, diglycerides, dipropylene glycol, eugenol, diacetin, diethanolamine, monoacetin, monoglycerides, PEG vegetable oil, N,N-dimethylformamide, N-methyl formamide, N-methylacetamide, N,N-dimethylacetamide, or combinations thereof.

Glycol ethers are organic solvents that are moderately soluble to miscible with water and can be used as a solvent in formation of a composition used in the methods described herein. A glycol ether is an ether formed from at least one glycol and at least one lower alkyl alcohol. Preferably the glycol is selected from an alkylene glycol such as ethylene glycol, propylene glycol, and butylene glycol. The ether portion of the glycol ether is a radical of a lower alkyl alcohol such as a C_1 to C_6 alcohol. Preferably, the ether portion alcohol is selected from methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, and isobutyl alcohol.

Examples of glycol ethers under the classification of ethylene glycol ethers include ethylene glycol monopropyl ether (propoxyethanol), ethylene glycol monobutyl ether (butoxyethanol), diethylene glycol monoethyl ether (ethoxydiglycol, DGME), diethylene glycol monobutyl ether (butoxydiglycol), diethylene glycol monoisopropyl ether (isopropyldiglycol), and diethylene glycol monoisobutyl ether (isobutyl diglycol).

Glycol ethers under the classification of propylene glycol ethers include propylene glycol monomethyl ether, dipropylene glycol monomethyl ether (PPG-2 methyl ether), tripropylene glycol monomethyl ether (PPG-3 methyl ether), propylene glycol n-propyl ether, dipropylene glycol n-propyl ether (PPG-2 propyl ether), propylene glycol monobutyl ether, dipropylene glycol monobutyl ether (PPG-2 butyl ether), propylene glycol monoisobutyl ether, and dipropylene glycol dimethyl ether. In one embodiment of the invention the

solvent is ethoxydiglycol. Additional suitable exemplary glycol ethers are disclosed, e.g., in Aldrich Handbook of Fine Chemicals, 2003-2004 (Milwaukee, WI).

In some embodiments, compositions of the invention have a glycol ether present in about 20 wt.% to about 40.0 wt.%. In some embodiments, compositions of the invention have a glycol ether present in about 20.0 wt.% to about 35.0 wt.%. In some embodiments, compositions of the invention have a glycol ether present in about 25.0 wt.% to about 40.0 wt.%. In yet another embodiment, compositions of the present invention have a glycol ether present in about 25.0 wt.% to about 35.0 wt.% of the composition. More specifically, compositions of the present invention have a glycol ether present in about 25.0 wt.% of the composition.

Additives

Preservatives may also be used in the pharmaceutical composition and preferably comprise about 0.05% to 0.5% by weight of the total composition. The use of preservatives assures that if the product is microbially contaminated, the formulation will prevent or diminish microorganism growth. Some preservatives useful in the pharmaceutical composition include methylparaben, propylparaben, butylparaben, chloroxylenol, sodium benzoate, DMDM Hydantoin, 3-Iodo-2-Propylbutyl carbamate, potassium sorbate, chlorhexidine digluconate, or a combination thereof.

Titanium dioxide may be used as a sunscreen to serve as prophylaxis against photosensitization. Alternative sunscreens include methyl cinnamate. Moreover, BHA may be used as an antioxidant, as well as to protect ethoxydiglycol and/or dapsone from discoloration due to oxidation. An alternate antioxidant is BHT.

Preferred formulations

As described herein, rosacea is treated by topically applying a topical composition comprising dapsone. In some embodiments, the topical composition comprises dissolved dapsone. In preferred embodiments, the topical composition is a pharmaceutical carrier system that is an aqueous gel, wherein the composition exhibits an optimal balance between dissolved dapsone that is available to cross through the stratum corneum to become systemically available, and microparticulate dapsone that is retained above the stratum

corneum to serve as a reservoir or to provide dapsone to the supracorneum zone, crossing the stratum corneum of the epidermis only minimally as a solid. The solid microparticulate dapsone reservoir is slowly dissolved in body fluids and then delivered through the stratum corneum. In some embodiments, the microparticulate dapsone is any solid form of dapsone that is added to a saturated solution of dapsone. In other embodiments, the microparticulate dapsone may be a precipitate formed by the addition of water to a solution containing a solvent and dapsone. The precipitate may comprise a crystalline precipitate or an amorphous precipitate.

Optimal balance is accomplished by having a gel carrier system in which microparticulate dapsone is formed in reproducible ratios with respect to the dissolved dapsone. For the composition to have a wide range of applicability, the microparticulate to dissolved dapsone ratio preferably should be no greater than five, at therapeutic levels of applied active dapsone.

A composition having a microparticulate to dissolved dapsone ratio of less than two may provide the greatest amount of pharmaceutical available for immediate partition out of the stratum corneum and into the viable epidermis. This should provide minimum reservoir capacity, and may not maintain sustained delivery or provide maximum activity in the supracorneum zone. A composition having a microparticulate to dissolved dapsone ratio of two or greater may have a reduced amount of drug available for immediate partition out of the stratum corneum and into the viable epidermis. This provides maximum reservoir capacity, maintains sustained delivery through the stratum corneum by slowly dissolving the dapsone in body fluids, and provides activity in the supracorneum zone. For the present invention, the ratio for microparticulate drug to dissolved drug should be no greater than 50, and preferably no greater than 10. More preferably, the ratio for microparticulate drug to dissolved drug should be no greater than 7 or no greater than 6. Most preferably, the ratio for microparticulate drug to dissolved drug should be about 5.5, 5.4, 5.3, 5.2, 5.1 or 5.0. In some embodiments, the ratio for microparticulate drug to dissolved drug should be no greater than 5. Drug delivery from the microparticulate/dissolved dapsone formulation may be optimized to provide higher levels of drug to the supracorneum zone, while maintaining the level of drug partitioning through the

stratum corneum and into the viable epidermis, despite 10-fold increases in the amount of pharmaceutical applied to the topical surface.

The compositions of the present invention comprise semi-solid and gel-like vehicles that include a thickener, water, preservatives, active surfactants or emulsifiers, antioxidants, sunscreens, and a solvent or mixed solvent system. The solvent or mixed solvent system is important to the formation of the microparticulate to dissolved dapsone ratio. The formation of the microparticulate, however, should not interfere with the ability of the thickener or preservative systems to perform their functions.

In a preferred embodiment, the topical composition comprises a thickening agent; water; a high-boiling, nonionic organic solvent; a preservative; dapsone in a microparticulate and dissolved state; and a base solution. In one embodiment, the topical composition that is applied includes about 0.5% to 4.0% carbomer and about 0.5% to 10% of dapsone that exists in both a dissolved state and a microparticulate state. The dissolved dapsone has the capacity to cross the stratum corneum, whereas the microparticulate dapsone does not. Addition of an amine base, potassium hydroxide solution, or sodium hydroxide solution completes the formation of the gel. A preferred ratio of microparticulate to dissolved dapsone is approximately five, which includes 5.5, 5.4, 5.3, 5.2, 5.1 and 5.0.

In some embodiments, the topical composition comprises about 5% dapsone, about 4% dapsone, about 3% dapsone, about 2% dapsone, or about 1% dapsone. In other embodiments, the topical composition comprises between 0.5% and 5% dapsone. In still other embodiments, the topical composition comprises between 0.5% and 10% of dapsone. In another embodiment, the pharmaceutical composition comprises about 1% carbomer, about 80-90% water, about 10% ethoxydiglycol (DGME), about 0.2% methylparaben, about 0.3% to 3.0% dapsone including both microparticulate dapsone and dissolved dapsone, and about 2% caustic material. More particularly, the carbomer may include "CARBOPOL® 980" and the caustic material may include sodium hydroxide solution.

In another embodiment, the composition comprises dapsone and ethoxydiglycol (DGME), which allows for an optimized ratio of microparticulate drug to dissolved drug. This ratio determines the amount of drug delivered,

compared to the amount of drug retained above the stratum corneum to function as a reservoir or for action in the supracorneum domain. The system of dapsone and ethoxydiglycol may include purified water combined with "CARBOPOL®" gelling polymer, methylparaben, propylparaben, titanium dioxide, BHA, and a caustic material to neutralize the "CARBOPOL®."

In a preferred embodiment, the composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide; and about 68.75% purified water.

The relative percentages for each of the reagents used in the pharmaceutical composition may vary depending upon the desired strength of the target formulation, gel viscosity, and the desired ratio of microparticulate to dissolved dapsone. Unless otherwise designated, all reagents listed above are commonly known by one of ordinary skill in the art and are commercially available from pharmaceutical or cosmetic excipient suppliers.

Additional agents for combination therapy

It is contemplated that the methods described herein may include the use of other topical formulations in combination with topical dapsone. There are a number of specific courses of treatment that can be carried out. In some embodiments, the dapsone topical formulation and other topical formulation are administered simultaneously. In other embodiments, the dapsone topical formulation and other topical formulation are administered sequentially. Over the course of treatment, the administration of one formulation can continue when the other is discontinued and vice versa.

It is further contemplated that the methods described herein may include the use of other active pharmaceutical ingredients in combination with dapsone in a single topical composition. In these embodiments, the dapsone and other active ingredient are administered simultaneously.

Other topical formulations and active agents contemplated to be employed in conjunction with topical dapsone include, but are not limited to, metronidazole, azelaic acid, sodium sulfacetamide/sulfur preparations, and antibiotics including erythromycin, clindamycin and tetracycline. In one combination regimen, dapsone is applied in the AM and metronidazole is

applied in the PM. In another combination regimen, metronidazole is applied in the AM and dapsone is applied in the PM.

It is further contemplated that the methods described herein include the use of systemic rosacea therapy in combination with topical dapsone therapy. Contemplated systemic therapies for use in combination with topical dapsone therapy include, but are not limited to, oral metronidazole and isotretinoin, and tetracyclines including doxycycline.

In one specific embodiment of the invention, the dapsone composition can be co-administered with photochemotherapy with ultraviolet A (PUVA). In another specific embodiment of the invention, the dapsone compositioncan be co-administered with phototherapy with UVB. As used herein, "photochemotherapy with ultraviolet A (PUVA)" refers to a type of ultraviolet radiation treatment (phototherapy) used for severe skin diseases. PUVA is a combination treatment which consists of Psoralen (P) administration and then exposure of the skin to long wave ultraviolet radiation (UVA).

Dapsone plasma levels

An advantage of the methods described herein is that blood plasma levels of dapsone and metabolites including N-acetyl dapsone and N-hydroxylamine dapsone are greatly reduced in comparison to oral administration of dapsone. The methods described herein employing topical dapsone are contemplated to result in blood plasma levels of dapsone and metabolites including N-acetyl dapsone and N-hydroxylamine dapsone less than about 150 ng/mL, less than about 100 ng/mL, less than about 90 ng/mL, less than about 80 ng/mL, less than about 70 ng/mL, less than about 60 ng/mL, less than about 50 ng/mL, less than about 40 ng/mL, less than about 30 ng/mL, less than about 20 ng/mL, less than about 10 ng/mL, less than about 9 ng/mL, less than about 8 ng/mL, less than about 7 ng/mL, less than about 6 ng/mL, less than about 5 ng/mL, less than about 4 ng/mL, less than about 3 ng/mL, less than about 2 ng/mL, and less than about 1 ng/mL.

Methods for Preparing Dapsone Topical Compositions

Those skilled in the art will be familiar with formulation methods used in preparing topical solutions or suspensions, lotions, ointments, creams and other formulations described above.

In some embodiments of the invention, a composition having dissolved dapsone and microparticulate dapsone is generally prepared by completely dissolving dapsone in a solvent or solvent mixture; adding and adequately dispersing a polymeric thickener in water; and combining the dissolved dapsone with the dispersed polymeric thickener. Alternatively, water may be slowly added to the dissolved dapsone, followed by the addition of a polymeric thickener. Ethoxydigylcol (DGME) and 1-methyl-2-pyrollidone are preferred solvents for use in the topically applied composition.

In some embodiments of the invention, the composition having dissolved dapsone and microparticulate dapsone is prepared by first forming a liquid by combining an organic solvent and water, and then contacting dapsone in a microparticulate solid form with the liquid, such that the microparticulate solid dapsone form does not entirely dissolve in the liquid; and dissolving a thickener in the liquid at a concentration sufficient to form a gel. In another embodiment of the invention, the composition having dissolved dapsone and microparticulate dapsone is prepared by, prior to the step of contacting the microparticulate solid dapsone with the liquid, forming a solution of the dapsone in the liquid, wherein the dapsone is substantially completely dissolved in the liquid.

In a preferred embodiment, the method for preparing a topically applied composition having dissolved and microparticulate dapsone comprises the steps of forming a homogenous dispersion by stirring purified water vigorously enough to form a vortex and sifting gel polymer into the vortex formed in the water while continuing to stir; forming a pharmaceutical component by dissolving methyl paraben and/or propylparaben in ethoxydiglycol by mixing to form a solution, and mixing dapsone with the solution until the pharmaceutical is dissolved; mixing the pharmaceutical component with the homogenous dispersion to form a microparticulate dapsone dispersion; and adding a caustic material.

The order in which reagents are combined may be important, depending on the particular reagents necessary for the target mixture. For example, after a pharmaceutical such as dapsone is dissolved in a solvent such as ethoxydiglycol, water may be slowly added to the dapsone in the ethoxydiglycol solution, or the dapsone in ethoxydiglycol solution may be added to the water with mixing. Adding the dapsone in ethoxydiglycol solution to water may result in less

polydispersity in the size of the microparticulates than adding water to the dapsone in ethoxydiglycol solutions. The carbomer is generally dispersed in the water component of the formulation, while the remaining ingredients will be dissolved or dispersed in whichever of the two components are best for dissolving or dispersing the ingredient. For example, it is suggested to dissolve methylparaben, propylparaben, and BHA in ethoxydiglycol. After the ethoxydiglycol component and water component are combined, neutralizer is added to formulate the gel.

As described below, a study was conducted using as test subjects 399 male and female subjects ≥ 18 years of age. At baseline, the subjects had a diagnosis of papulopustular rosacea, with ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. There was an overall improvement from baseline in local symptom scores with treatment. While treatment showed efficacy for patients with ≥ 10 inflammatory lesions, improved results were shown for subjects who entered the study with ≥ 20 inflammatory papulopustular lesions. It was surprising that the treatment was more successful for a more severe form of the disease. Topical application of 5% dapsone is safe and well tolerated when used to treat subjects with papulopustular rosacea. Systemic levels of dapsone and its metabolites were low during the study with no evidence of increasing exposure over time. No subjects in the study demonstrated evidence of hemolysis or treatment related hematological adverse events.

The invention will be described by the following non-limiting example.

Example 1

Methods

A twelve week study was conducted in 399 male and female subjects ≥ 18 years of age. At baseline, the subjects had a diagnosis of papulopustular rosacea, with ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. Each subject had an Investigator Global Assessment (IGA) score ≥ 2, as defined in Table 1.

Table 1: Investigator Global Assessment of Disease Severity

Score	Severity	Description
0	Clear	No signs or symptoms present; at most, mild erythema
1	Almost Clear	Very mild erythema present. Very few small papules/pustules
2	Mild	Mild erythema. Several small papules/pustules
3	Moderate	Moderate erythema. Several small or large papules/pustules, and up to 2 nodules
4	Severe	Severe erythema. Numerous small and/or large papules/pustules, up to several nodules.

The subjects were randomly assigned to one of the following five treatment groups:

1) Vehicle Control (VC), 2x/day (80 subjects).
2) Aczone™ Gel, 5%, 2x/day (84 subjects).
3) Aczone™ Gel, 5%, 1x/day (79 subjects).
4) MetroGel® (metronidazole gel), 1%, 1x/day (80 subjects).
5) Aczone™ Gel, 5% 1x/day + MetroGel® (metronidazole gel), 1%, 1x/day (76 subjects).

MetroGel® is a 1% gel formulation of metronidazole. Metronidazole has been used as a topical therapy for rosacea since its approval in 1988 and is effective in reducing inflammatory papules and pustules and producing overall improvement in rosacea symptoms (Bikowski and Goldman, 2004).

MetroGel® contained the active ingredient metronidazole (10 mg per gram). Inactive ingredients in MetroGel® included: betadex, edetate disodium, hydroxyethyl cellulose, methylparaben, niacinamide, phenoxyethanol, propylene glycol, propylparaben, and purified water.

Aczone™ Gel is a 5% gel formulation of dapsone. Aczone™ gel contained the active ingredient dapsone (50 mg per gram). Inactive ingredients in the Aczone™ gel included: carbomer 980, diethylene glycol monoethyl ether (DGME), methylparaben, sodium hydroxide, and purified water. The vehicle control (VC) contained only the inactive components carbomer 980, diethylene glycol monoethyl ether (DGME), methylparaben, propylparaben, sodium hydroxide, and purified water.

The Aczone™ (dapsone 5%) gel was prepared as follows:

A polymer thickener component was prepared by charging 66.95 grams of purified water to a vessel suitable to contain 100 grams of finished semisolid

product, and 0.85 g of "CARBOPOL® 980" was slowly sifted into a vortex formed by rapidly stirring the purified water. When a homogeneous dispersion of "CARBOPOL® 980" and water was formed, stirring was reduced to minimize air entrapment. Next, an active pharmaceutical component was prepared by charging an appropriately sized container with 25 g of ethoxydiglycol, then 0.2 g of methylparaben were added to the ethoxydiglycol and mixed until all of the crystalline solid was dissolved. 5.0 g dapsone was added to the ethoxydiglycol and mixed until the drug was completely dissolved. The polymer thickener component was added to the pharmaceutical component with mixing, immediately resulting in the formation of crystalline microparticles. Once the dispersion was homogenous, 2.0 grams of a 10% w/w aqueous sodium hydroxide solution were added to neutralize the CARBOPOL® 980 and form the gel.

The application procedures for all treatment groups were the same. Subjects applied a thin film of the study treatment onto the entire face and rubbed gently until it completely disappeared, after first washing the face with a standard cleanser. For twice-daily regimens, applications occurred once in the morning (AM) and once in the evening (PM). For once-daily regimens, applications occurred in the evening (PM). For the combination regimen, dapsone was applied in the AM and MetroGel® was applied in the PM.

Efficacy assessments included monitoring inflammatory lesion counts, Investigator Global Assessment (IGA) scores, erythema scores, and telangiectasia scores. Plasma dapsone concentrations were measured to assess systemic exposure to the study treatment. Safety was evaluated by monitoring adverse events, hematology and serum chemistry parameters, concomitant medications, vital signs, and local symptoms (dryness, itching, stinging, and burning).

Success rates, based on changes from baseline lesion counts and on the 5-point IGA, are direct indications of treatment response, and have been used in recent studies of other rosacea therapies (Wilkin et al., 2004; Thiboutot et al., 2003). Both of these endpoints are considered important and clinically relevant in evaluating the efficacy of treatments for rosacea. Erythema and telangiectasia are signs of rosacea that were evaluated according to standardized 4-point scales, and treatment-induced changes in these signs were considered to be clinically

meaningful to subjects. Subjects were followed for 7 days after stopping treatment to monitor any ongoing adverse events.

Results

Inflammatory Lesion Counts. The change from baseline in inflammatory lesion counts, percent change from baseline in inflammatory lesion counts, and lesion counts over time were summarized by N, mean, standard deviation, median, minimum, and maximum. Summaries were provided separately for each treatment group and study visit. In addition, 95% confidence intervals were provided for each treatment group and for the difference between vehicle control (VC) and each active treatment group.

The change from baseline in inflammatory lesion counts for each study visit was calculated by subtracting the baseline inflammatory lesion count from the post baseline study visit lesion counts for each subject. The percent change from baseline in inflammatory lesion counts was calculated by dividing the baseline inflammatory lesion count into the change from baseline in inflammatory lesion counts and then multiplying by 100 for each subject at each study visit.

At baseline, the mean inflammatory lesion count for all treatment groups was 21.6. Figure 1 shows the mean change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean decrease from baseline in lesion counts. Squares, vehicle control; triangles, Aczone™ (dapsone 5%) 2x/day; inverted triangles, Aczone™ (dapsone 5%) 1x/day; diamonds, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with MetroGel® alone or dapsone + MetroGel® experienced the largest mean decreases from baseline (–11.3 and –11.4 lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean decrease from baseline (–5.7 lesions from baseline). The mean change from baseline in the dapsone 2x/day group (–8.0 lesions) was higher than the dapsone 1x/day group, but similar to the VC group (–8.3 lesions), which was observed to decrease the number of inflammatory lesions.

A review of historical results for other approved therapies shows that the mean changes from baseline in lesion count for the dapsone 2x/day group was close to that of other approved products for rosacea, including Finacea® (azelaic acid) Gel, 15%, Oracea® (doxycycline) 40 mg capsules, and the active comparator in this study, MetroGel® (metronidazole), 1.0%. The changes from baseline in inflammatory lesion counts for Finacea® were reported as –10.7 and –8.9 (differences of 3.6 and 2.5 lesions in favor of active treatment over vehicle) (Finacea® package insert, 2005). For Oracea®, the changes from baseline in lesion counts were –11.8 and –9.5 (differences of 5.9 and 5.2 lesions in favor of active treatment over vehicle) (Oracea® package insert, 2006). Historically, subjects treated with the 1% strength of MetroGel® once-daily demonstrated a reduction in lesion count from baseline of –9.4 lesions, with a difference of 5.6 lesions over vehicle (MetroGel® package insert, 2005). The historical response for MetroGel® was less than the response observed in this study (–11.3 lesion decrease from baseline), which is most likely due to differences in study conditions and the fewer numbers of subjects enrolled in this study. In the intent-to-treat (ITT) analysis, treatment with the combination of MetroGel® and dapsone was not different from treatment with MetroGel® alone by Week 12 in terms of lesion count reduction.

Figure 2 shows the mean percent change from baseline in inflammatory lesion counts in the intent to treat (ITT) population having ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Subgroup Analysis: Subjects With <20 Lesions. The subgroup of subjects with <20 lesions at baseline was analyzed independently of the ITT group. For this subgroup, the baseline mean inflammatory lesion count ranged from 13.6 lesions to 14.3 lesions across treatment groups, with an overall mean of 14.0 lesions. Figure 3 depicts the mean change from baseline in lesion counts for this subgroup of subjects with <20 lesions at baseline. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 2x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day;

circles, Aczone™ 1x/day + MetroGel® 1x/day. Subjects in all treatment groups experienced a mean decrease from baseline in inflammatory lesion count. In this subgroup at week 12, the MetroGel® alone 1x/day experienced a mean decrease of -7.7 lesions; the dapsone + MetroGel® group experienced a mean decrease of -7.2 lesions; the vehicle control (VC) experienced a mean decrease of -6.0 lesions; and the dapsone 2x/day and dapsone 1x/day groups experienced a mean decrease of -3.6 lesions.

Figure 4 shows the mean percent change from baseline in inflammatory lesion counts in the subgroup population having <20 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with MetroGel® (metronidazole 1%) 1x/day or Aczone™ 1x/day + MetroGel® 1x/day experienced the largest mean percent decreases from baseline (55.3% and 52.0% mean reductions in lesions, respectively), while the vehicle control group experienced a 41.9% mean reduction in lesions. The dapsone 1x/day group experienced a 27.7% mean reduction in lesions and the dapsone 2x/day experienced a 23.3% mean reduction in lesions.

Subgroup Analysis: Subjects With ≥ 20 Lesions. The subgroup of subjects with ≥ 20 lesions at baseline was analyzed independently of the ITT group. The cut-off of 20 lesions was chosen as the number which most closely approximated the baseline mean lesion count in subjects who entered the study with a baseline IGA in the moderate or severe categories. The size of this subgroup was relatively large (42% of the ITT population).

For this subgroup, the baseline mean inflammatory lesion count ranged from 28.4 lesions to 33.8 lesions across treatment groups, with an overall mean of 32.1 lesions. Figure 5 depicts the mean change from baseline in lesion counts for this subgroup of subjects with ≥ 20 lesions at baseline. Squares, vehicle control; triangles, Aczone™ (dapsone 5%) 2x/day; inverted triangles, Aczone™ (dapsone 5%) 1x/day; diamonds, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. Subjects in all treatment groups experienced a mean decrease from baseline in inflammatory lesion count that

was higher than the overall mean decrease for the ITT population. In this subgroup, the dapsone 2x/day, MetroGel®, and dapsone + MetroGel® groups experienced the highest mean decreases by Week 12 (–15.5, –15.5, and –15.6 lesions respectively). The dapsone 1x/day and VC groups, respectively, experienced mean decreases of –9.3 and –11.6 lesions. Comparing the dapsone 2x/day and Vehicle Control groups, there was a 3.9 lesion difference in the mean decrease from baseline in favor of dapsone, similar to the differences between active and vehicle for other approved treatments (as described above).

Figure 6 shows the mean percent change from baseline in inflammatory lesion counts in the subgroup population having ≥ 20 inflammatory lesions (papules and/or pustules) above the mandibular line. All study treatment groups experienced a mean percent decrease from baseline in lesion counts. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At Week 12, subjects treated with dapsone 2x/day, MetroGel® 1x/day, and dapsone + MetroGel® experienced the largest mean percent decreases from baseline (58.4%, 46.6% and 45.0% reduction in lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean percent decrease from baseline (20.9% decrease in lesions from baseline). The mean percent change from baseline in the vehicle control group was 42.3%.

IGA Success. The IGA score and success rate from the IGA were summarized by frequencies and percents. Success rate was defined as the proportion of subjects with a score of 0 (clear) or 1 (almost clear) and at least a 2 point improvement from baseline on the 5-point Investigator's Global Assessment (IGA) scale of disease severity. In addition, 95% confidence intervals were calculated for the success rate from the IGA for each treatment group and for the difference between VC and each active treatment group.

At baseline, most subjects had an IGA score of moderate (62% for all subjects combined). The distribution of IGA scores shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. Figure 7 shows the IGA success rate over the course of the study in the intent to treat (ITT) population

having ≥ 10 inflammatory lesions. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (5.1% to 19.7%) or almost clear (25.0% to 33.8%). Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Figure 8 summarizes the IGA success rate at week 12 in the intent to treat (ITT) population having ≥ 10 inflammatory lesions. At 12 weeks, the success rate was highest in the dapsone + MetroGel® group (39.5%) and lowest in the dapsone 1x/day group (24.1%). The success rate in the dapsone 2x/day group was higher than the dapsone 1x/day group but the rate was very similar to VC (27.4% and 27.5%, respectively). The combination treatment group experienced higher success than either the MetroGel® alone (32.5%) or the dapsone 1x/day (24.1%).

Subgroup Analysis: Subjects With <20 Lesions. At baseline, 56% of the subjects with <20 lesions had a moderate score on the IGA, while 41% had a mild score on the IGA. The distribution of IGA scores in subjects with <20 lesions at baseline shifted towards improvement over the 12 weeks for all study treatments. Figure 9 shows the IGA success rate over the course of the study in subjects with <20 lesions. Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day. At week 12, approximately 40% to 60% of the subjects enrolled in each group had an IGA score of clear (4.0% to 26.3%) or almost clear (29.8% to 42.0%).

Subgroup Analysis: Subjects With ≥ 20 Lesions. At baseline, most subjects with ≥ 20 lesions had a moderate score on the IGA (70%). Similar to the ITT analysis, the distribution of IGA scores in subjects with ≥ 20 lesions at baseline shifted towards improvement as early as Week 2 for all study treatments, where the percentages of subjects with scores of moderate or severe decreased and percentages of subjects with scores of mild or almost clear increased. Figure 10 shows the IGA success rate over the course of the study in subjects with ≥ 20 lesions. At Week 12, approximately one third to one half of the subjects enrolled in each group had an IGA score of clear (6.5% to 13.2%) or

almost clear (17.2% to 29.7%). Diamonds, vehicle control; light squares, Aczone™ (dapsone 5%) 2x/day; triangles, Aczone™ (dapsone 5%) 1x/day; dark squares, MetroGel® (metronidazole 1%) 1x/day; circles, Aczone™ 1x/day + MetroGel® 1x/day.

Figure 11 summarizes the IGA success rate for this subgroup at week 12. The percentage of subjects with ≥ 20 lesions who had treatment success at Week 12 was highest in the dapsone + MetroGel® group (39.5%) and lowest in the VC group (21.2%). Success rates were better in the dapsone 2x/day group (32.3%) than either the dapsone 1x/day group (24.1%) or the VC (21.2%), equivalent to an 11.1% difference favoring dapsone 2x/day treatment. Comparing the dapsone + MetroGel® group to the MetroGel® alone group, there was a higher success rate for the combination treatment (39.5% compared to 29.7%).

Erythema assessment. Erythema assessment scores were summarized by frequencies and percents. Erythema was graded according to the standardized scale shown in Table 2, at Day 0 (baseline) and Weeks 2, 4, 8, and 12.

TABLE 2. Erythema Assessment

Score	Severity	Description
0	Absent	No perceptible erythema.
1	Mild	Slight erythema with either restricted central involvement or generalized whole face.
2	Moderate	Pronounced erythema with either restricted central involvement or generalized whole face.
3	Severe	Severe erythema or red-purple hue with either restricted central involvement or generalized whole face.

At baseline, all subjects had at least mild erythema present (16.5% to 23.8%) with the majority displaying moderate erythema (60.0% to 70.9%). In general, erythema scores improved throughout the study, with 4.8% to 9.2% of subjects exhibiting no erythema at Week 12. There were no consistent differences in the distribution of erythema scores across study treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions. For the subgroup of subjects with ≥ 20 lesions, erythema was predominantly moderate at baseline. The distribution of erythema scores tended to shift towards improvement as the study progressed in all treatment groups. By Week 12, approximately half of the

subjects in each group had improved to a score of absent (3.2% to 9.1%) or mild (31.6% to 51.4%) from mostly moderate at baseline (58.1% to 82.8%). There were no consistent differences between the treatment groups.

Telangiectasia Assessment. Telangiectasia assessment scores were summarized by frequencies and percents. Telangiectasia was graded according to the standardized scale shown in Table 3 at Day 0 (baseline) and Weeks 2, 4, 8, and 12.

TABLE 3. Telangiectasia Assessment

Score	Severity	Description
0	Absent	No perceptible telangiectasia.
1	Mild	Involvement of the nose.
2	Moderate	Involvement of the nose and infraorbital region.
3	Severe	Involvement of the nose, infraorbital region, and other areas of the face.

At baseline, telangiectasia was predominantly moderate (41.7% to 57.5% of subjects). Throughout the study, there was a small shift towards improvement of telangiectasia, demonstrated by an increase in the percentages of subjects with absent or mild telangiectasia and decreases in the percentages of subjects with moderate or severe telangiectasia. At Week 12, approximately half of the subjects in each group had either absent (13.1% to 19.7%) or mild telangiectasia (34.2% to 43.8%). There were no consistent differences in the distribution of telangiectasia scores across study treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions. At baseline, the telangiectasia score was predominantly mild in subjects with ≥ 20 lesions in the dapsone 2x/day group (51.6%) and moderate (48.3% to 63.6%) for other treatments. This pattern was still evident at Week 12; however the percentages of subjects with moderate or severe telangiectasia generally decreased while the percentages of subjects with mild or absent generally increased.

Adverse Events. Application site adverse events were the most common type of adverse event reported. The majority of application site adverse events (dryness, itching, stinging, and burning) are signs and symptoms of rosacea that were solicited and scored using the standardized grading system shown in Table 4.

TABLE 4. Local Symptoms Assessment (Dryness, Itching, Stinging, and Burning)

Score	Severity	Description
0	Absent	None
1	Mild	Barely perceptible
2	Moderate	Definitely present
3	Severe	Marked, intense

The most frequent application site adverse event was dryness, which occurred at a similar frequency among study treatment groups (32.5% to 36.7%) and was typically mild to moderate in intensity. Other application site adverse events were pain (8.0% to 29.1%), burning (10.7% to 27.8%), pruritis (8.0% to 22.8%), and erythema (9.1% to 13.9%). The frequency of these application site adverse events was numerically lower in groups treated with MetroGel® alone or MetroGel® + dapsone compared with the vehicle control or dapsone-only treated groups. For all groups, the intensity of application site pain, burning, and pruritus was mostly mild while the intensity of application site erythema was mostly moderate to severe. The higher severity of application site erythema compared with other signs/symptoms of rosacea may be explained by the presence of erythema at baseline (which was mostly moderate) as part of the underlying rosacea characteristics whereas other local signs and symptoms were mostly absent or mild.

Skin and Subcutaneous Disorders occurred at a frequency ranging from 12.0% to 20.8%. The frequency was higher in the MetroGel® group (20.8%) compared with other groups (12.0% to 17.7%). Telangectasia, reported as a worsening of baseline telangiectasia that was part of the subject's underlying rosacea, was the only adverse event to occur with a frequency higher than 1% (10.8% to 14.3%). The incidence of telangiectasia was slightly higher in groups treated with MetroGel® or MetroGel® + dapsone than the vehicle or dapsone-only treated group.

Blood plasma dapsone levels. The amounts of dapsone and metabolites N-acetyl dapsone and N-hydroxylamine dapsone in plasma were measured at baseline, Week 2, Week 4, and Week 12 of the study. Mean plasma concentrations of dapsone and metabolites were low in study treatment groups

using Aczone™ at all time points measured in the study. The highest mean plasma concentrations were observed at Week 2, where subjects had a mean dapsone concentration of 10.6 ng/mL, 7.0 ng/mL, and 6.1 ng/mL in the Aczone™ 2x/day group, Aczone™ 1x/day group, and Aczone™ + MetroGel group, respectively. The maximum plasma concentration of dapsone observed in any subject was 87.43 ng/mL, at Week 2 (Aczone™ 2x/day group). Plasma concentrations of N-acetyl dapsone were also highest at Week 2 (means of 4.9, 3.1, and 2.9 ng/mL in the Aczone™ 2x/day, Aczone™ 1x/day, and combination groups respectively). Plasma concentrations of the hydroxylamine metabolite, which is believed to be the primary factor associated with dapsone hematological toxicities, were much lower than the parent (mean values <1 ng/mL in all Aczone™-treated groups, maximum in any subject using Aczone™ 2x/day was 6.7 ng/mL).

In subjects treated with the combination of Aczone™ and MetroGel, plasma levels of dapsone and metabolites were similar to or lower than subjects treated with the same amount of Aczone™ only (1x/day), suggesting that there are no pharmacokinetic interactions between these two drugs.

Subjects with G6PD-deficiency are known to be at higher risk of developing dapsone-related hematological toxicities following oral dapsone use. In this study, 1 subject with G6PD-deficiency was enrolled and treated with Aczone™ (1x/day). When measured at Weeks 2, 4, and 12, the subject's plasma dapsone levels were approximately 11 to 12 ng/mL and hydroxylamine levels <1 ng/mL. The subject's laboratory data does not reveal any changes from baseline over the course of the study, except for slightly elevated non-fasting blood glucose at Week 4 and slightly low monocyte counts at Weeks 2 and 4 that were not deemed to be clinically significant. There were no changes in any hematological parameters. Furthermore, there were no adverse events reported indicative of systemic dapsone toxicity; only mild, transient application site adverse events were reported by this subject.

Systemic exposure to dapsone and its metabolites was low at all time points in the study. Similar mean values for hemoglobin, hematocrit, red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, reticulocyte count, total bilirubin, haptoglobin, and LDH between baseline and Week 12 were shown across all treatment groups. There were no overall changes in any

chemistry or hematology parameter observed during the study. These findings demonstrate the low incidence of systemic adverse events with topical dapsone use and support the safety of using topical dapsone, as well as dapsone in combination with MetroGel®, in subjects with papulopustular rosacea.

Discussion

The efficacy of dapsone in treating subjects with papulopustular rosacea was investigated. Two dapsone-alone dosage regimens (1x/day and 2x/day) were employed, as was a dapsone + MetroGel® regimen (1x/day). The study was controlled with the dapsone vehicle applied 2x/day (VC) and with MetroGel® alone (applied 1x/day).

Baseline characteristics were generally similar across study treatment groups, except the percentage of patients who had severe telangiectasia at baseline was more variable (6% in the Vehicle and MetroGel® groups, 20% and 15% in the dapsone 2x/day and 1x/day respectively, and 17% in the dapsone + MetroGel® group).

All treatment groups experienced a mean decrease from baseline in lesion counts. At Week 12, subjects treated with MetroGel® alone or dapsone + MetroGel® experienced the largest mean decreases from baseline in lesion counts (–11.3 and –11.4 lesions, respectively) while subjects in the dapsone 1x/day group experienced the least mean decrease from baseline (–5.7 lesions). The mean change from baseline in the dapsone 2x/day group (–8.0 lesions) was higher than the dapsone 1x/day group, but similar to the vehicle control (VC) group (–8.3 lesions).

Success rates, defined as a score of clear or almost clear with at least 2 points of improvement on a 5-point IGA scale, showed that more subjects treated with dapsone 2x/day had success (27.4%) than subjects treated with dapsone 1x/day (24.1%), but there was no difference from VC (27.5%). The success rate for the combination treatment of dapsone + MetroGel® was higher than MetroGel® alone (39.5% success rate compared with 32.5%).

Erythema and telangiectasia were evaluated, using a standardized 4-point grading system. Both erythema and telangiectasia improved, though not substantially, in all study treatment groups by Week 12. There were no apparent differences in erythema and telangiectasia between treatment groups.

Subgroup Analysis: Subjects With ≥ 20 Lesions At Baseline. Subjects with ≥ 20 lesions in all treatment groups experienced a greater mean decrease from baseline in inflammatory lesion count than the overall mean decrease for the ITT population having ≥ 10 inflammatory lesions and the subgroup having <20 inflammatory lesions. This result was surprising because a milder form of the disease would be expected to show similar or improved treatment results compared to a more severe form of the disease. In this subgroup of subjects with ≥ 20 lesions, the dapsone 2x/day, MetroGel®, and dapsone + MetroGel® groups experienced the highest mean decreases by Week 12 (–15.5, –15.5, and –15.6 lesions respectively, corresponding to 58.4%, 46.6% and 45.0% reductions from baseline in lesions, respectively). The VC group experienced a mean decrease of –11.6 lesions (a 42.3% decrease) and the dapsone 1x/day group experienced a mean decrease of –9.3 lesions (a 20.9% decrease in lesions from baseline) at 12 weeks. Comparing the dapsone 2x/day and VC groups, there was a 3.9 lesion difference in the mean decrease from baseline in favor of dapsone.

In the ≥ 20 lesions subgroup, success at Week 12 was highest in the dapsone + MetroGel® group (39.5%) and lowest in the VC group (21.2%). Success rates were better in the dapsone 2x/day group (32.3%) than either the dapsone 1x/day group (24.1%) or the VC group (21.2%), equivalent to an 11.1% difference favoring dapsone 2x/day treatment. Comparing the dapsone + MetroGel® group to the MetroGel® alone group, there was a higher success rate for the combination treatment (39.5% compared to 29.7%)

Systemic exposure to dapsone and its metabolites was low at all time points in the study. Treatment with dapsone was safe and well tolerated in subjects with papulopustular rosacea. Most adverse events were at the application site, were mild, and were transient. Systemic adverse events were infrequent and were generally indicative of the common cold or flu. The most frequent adverse events were application site events including dryness, pain, burning, pruritis, and erythema, which are also known signs and symptoms of rosacea.

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All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification, this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED IS:

1. A method to treat rosacea comprising topically administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

2. The method of claim 1 wherein the rosacea is papulopustular rosacea.

3. The method of claim 2 wherein the papulopustular rosacea is mild to severe papulopustular rosacea.

4. The method of claim 2 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

5. The method of claim 2 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

6. The method of claim 2 wherein treatment results in a mean reduction of at least 43 % of the papulopustular lesions.

7. The method of claim 2 wherein the patient has 20 or more inflammatory lesions.

8. The method of claim 7 wherein the pharmaceutical composition is administered twice daily.

9. The method of claim 8 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

10. The method of claim 1 wherein the rosacea is ocular rosacea.

11. The method of claim 1 wherein said pharmaceutical composition is a semisolid aqueous gel.

12. The method of claim 1 wherein said pharmaceutical composition is a cream, lotion, suspension, ointment or spray.

13. The method of claim 1 wherein the pharmaceutical composition additionally comprises a thickening agent, a high-boiling, nonionic organic solvent, a preservative, or a base agent.

14. The method of claim 1 wherein the dapsone comprises about 0.5% to 10% of the pharmaceutical composition.

15. The method of claim 1 wherein the dapsone is present in both a microparticulate state and a dissolved state.

16. The method of claim 15 wherein the microparticulate dapsone is a crystalline precipitate.

17. The method of claim 15 wherein the microparticulate dapsone is an amorphous precipitate.

18. The method of claim 1 wherein the pharmaceutical composition further comprises an antioxidant, a fragrance, a colorant, a sunscreen, or combinations thereof.

19. The method of claim 1 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide; and about 68.75% purified water.

20. The method of claim 1 further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier.

21. The method of claim 20 wherein the metronidazole is included in the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

22. The method of claim 20 wherein the metronidazole is administered separately from the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

23. The method of claim 1 wherein the pharmaceutical composition is administered twice daily.

24. A method to treat rosacea comprising topically administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier, wherein plasma levels of dapsone remain less than about 100 ng/mL.

25. The method of claim 24 wherein the rosacea is ocular rosacea.

26. The method of claim 24 wherein the rosacea is papulopustular rosacea.

27. The method of claim 26 wherein the papulopustular rosacea is mild to severe papulopustular rosacea.

28. The method of claim 26 wherein the rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

29. The method of claim 26 wherein the patient has 20 or more inflammatory lesions.

30. The method of claim 29 wherein the pharmaceutical composition is administered twice daily.

31. The method of claim 30 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

32. The method of claim 26 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

33. The method of claim 26 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

34. The method of claim 24 wherein said pharmaceutical composition is a semisolid aqueous gel.

35. The method of claim 24 wherein said pharmaceutical composition is a cream, lotion, suspension, ointment or spray.

36. The method of claim 24 wherein the pharmaceutical composition additionally comprises a thickening agent, a high-boiling, nonionic organic solvent, a preservative, or a base agent.

37. The method of claim 24 wherein the dapsone comprises about 0.5% to 10% of the pharmaceutical composition.

38. The method of claim 24 wherein the dapsone is present in a microparticulate and a dissolved state.

39. The method of claim 38 wherein the microparticulate dapsone is a crystalline precipitate.

40. The method of claim 38 wherein the microparticulate dapsone is an amorphous precipitate.

41. The method of claim 24 wherein said pharmaceutical composition further comprises an additive selected from the group consisting of an antioxidant, a fragrance, a colorant, and a sunscreen.

42. The method of claim 24 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

43. The method of claim 24 further comprising administering a composition comprising metronidazole.

44. The method of claim 43 wherein the metronidazole is included in the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

45. The method of claim 43 wherein the metronidazole is administered separately from the pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

46. The method of claim 24 wherein the pharmaceutical composition is administered twice daily.

47. A method to treat papulopustular rosacea comprising topically administering to a patient having at least ten rosacea lesions an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

48. The method of claim 47, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

49. The method of claim 48, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

50. A method to treat papulopustular rosacea comprising topically administering to a patient having at least twenty rosacea lesions an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

51. The method of claim 50, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

52. The method of claim 51, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

53. The method of claim 50 wherein the pharmaceutical composition is administered twice daily.

54. The method of claim 53 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

55. The method of claim 50 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

56. The method of claim 50 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions

57. A method to treat rosacea comprising applying topically a semisolid gel composition, the semisolid gel composition comprising:

a semisolid aqueous gel; and

dapsone partially in a microparticulate form and partially dissolved in said semisolid aqueous gel.

58. The method of claim 57 wherein the rosacea is mild to severe papulopustular rosacea.

59. The method of claim 57 wherein the rosacea includes 20 or more papulopustular lesions.

60. The method of claim 59 wherein the semisolid gel composition is administered twice daily.

61. The method of claim 60 wherein the semisolid gel composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

62. The method of claim 57 wherein the rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

63. The method of claim 59 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

64. The method of claim 59 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

65. A method to treat rosacea comprising topically applying a gel composition comprising dissolved dapsone and a microparticulate dapsone, wherein:

the dissolved dapsone crosses the stratum corneum of the epidermis and is absorbed into the lower two-thirds of the pilosebaceous unit; and

the microparticulate dapsone is primarily delivered into the upper third of the pilosebaceous unit, crossing the stratum corneum of the epidermis only minimally as a solid.

66. The method of claim 65, wherein the rosacea is papulopustular rosacea.

67. The method of claim 66 wherein the papulopustular rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

68. The method of claim 66 wherein the rosacea includes 20 or more papulopustular lesions.

69. The method of claim 68 wherein the gel composition is administered twice daily.

70. The method of claim 69 wherein the gel composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

71. The method of claim 65, wherein the rosacea is ocular rosacea.

72. The method of claim 66 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

73. The method of claim 66 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

74. A method to reduce a number of papulopustular rosacea lesions comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

75. The method of claim 74 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

76. The method of claim 74, wherein the patient has at least twenty papulopustular rosacea lesions before administration of the pharmaceutical composition.

77. The method of claim 76, wherein the pharmaceutical composition is administered twice daily.

78. The method of claim 77 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

79. The method of claim 74, further comprising administering a composition comprising metronidazole and a pharmaceutically acceptable carrier to the patient.

80. The method of claim 79, wherein the composition comprising dapsone and a pharmaceutically acceptable carrier is administered

once daily and the composition comprising metronidazole and a pharmaceutically acceptable carrier is administered once daily.

81. The method of claim 74 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

82. The method of claim 74 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

83. A method to treat mild to severe papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

84. A method to treat papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier two times daily.

85. The method of claim 84 wherein the papulopustular rosacea comprises 20 or more lesions.

86. The method of claim 85 wherein the pharmaceutical composition comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

87. The method of claim 84 wherein the patient has an Investigator Global Assessment score of 3 or higher before treatment.

88. The method of claim 84 wherein treatment results in a mean reduction of at least 13 papulopustular lesions.

89. The method of claim 84 wherein treatment results in a mean reduction of at least 43% of the papulopustular lesions.

90. A method to treat papulopustular rosacea comprising administering topically to a patient in need thereof an effective amount of a pharmaceutical composition comprising dapsone and an effective amount of a pharmaceutical composition comprising metronidazole.

91. The method of claim 90 wherein the papulopustular rosacea comprises 20 or more lesions.

92. The method of claim 91 wherein the pharmaceutical composition comprising dapsone comprises about 5% dapsone, about 0.85% carbomer 980, about 25% diethylene glycol monoethyl ether (DGME), about 0.2% methylparaben, about 0.2% sodium hydroxide, and about 68.75% purified water.

93. The method of claim 90, wherein the papulopustular rosacea has an Investigator Global Assessment score of 3 or higher before treatment.

94. The method of claim 90 wherein the pharmaceutical composition comprising dapsone is administered once daily and the pharmaceutical composition comprising metronidazole is administered once daily.

95. The method of claim 90 wherein treatment results in a mean reduction of at least 14 papulopustular lesions.

96. The method of claim 90 wherein treatment results in a mean reduction of 43% of the papulopustular lesions.

97. A method to treat an ocular disease or disorder comprising topically administering to a patient in need thereof an effective amount of a

pharmaceutical composition comprising dapsone and a pharmaceutically acceptable carrier.

98. The method of claim 97 wherein the ocular disease or disorder is ocular rosacea.

99. The method of claim 97 wherein the ocular disease or disorder is ocular cicatrical pemphigoid.

100. The method of claim 97 wherein the ocular disease or disorder is selected from the group consisting of conjunctivitis, scleritis, nodular scleritis secondary to Sweet's syndrome, vasculitis, autoimmune vasculitis, retinal vasculitis of Eales' disease, uveitis, granulomatous uveitis, panuveitis, ocular leprosy, arachnid evenomation, Behçet disease, linear IgA disease, relapsing polychondritis, peripheral keratitis, tuberculosis, Hodgkin lymphoma, non-Hodgkin lymphoma, T-cell lymphoma, Reiter's syndrome, tumor of the eyelid, erythema elevatum diutinum, erosive lichen planus, and pneumocystis carinii choroiditis associated with AIDS

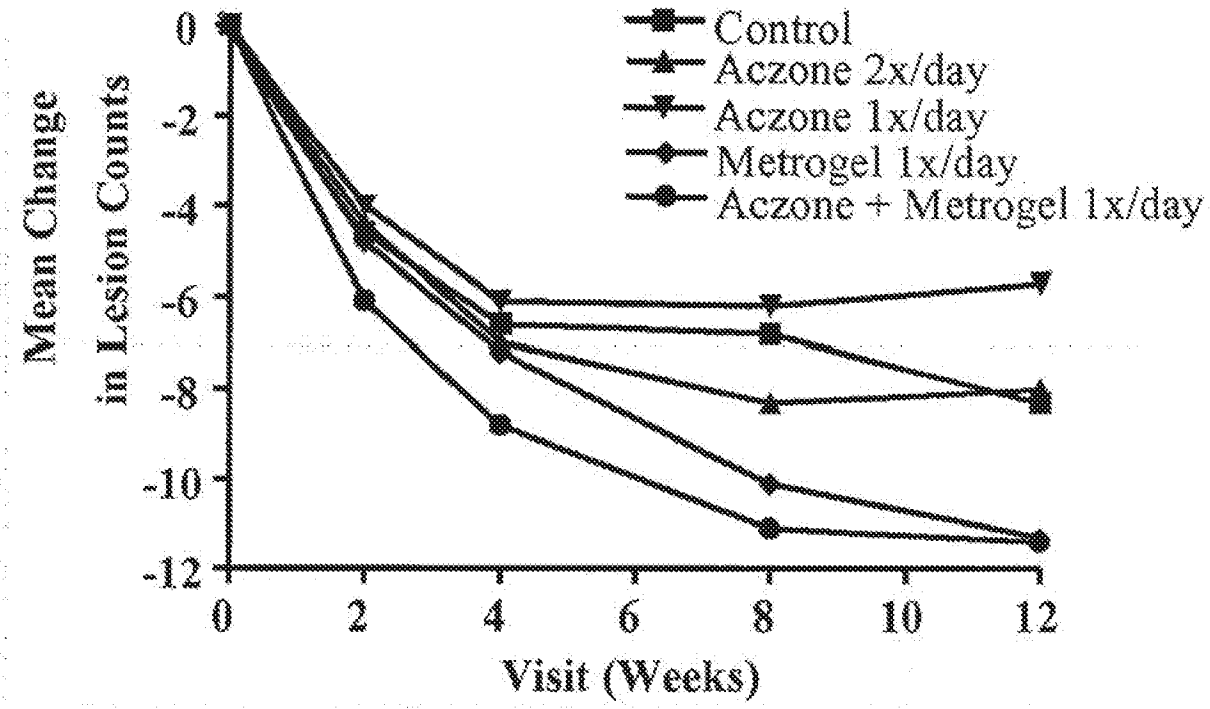
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
0
2
4
6
8
10
12
Visit (Weeks)

FIG. 1

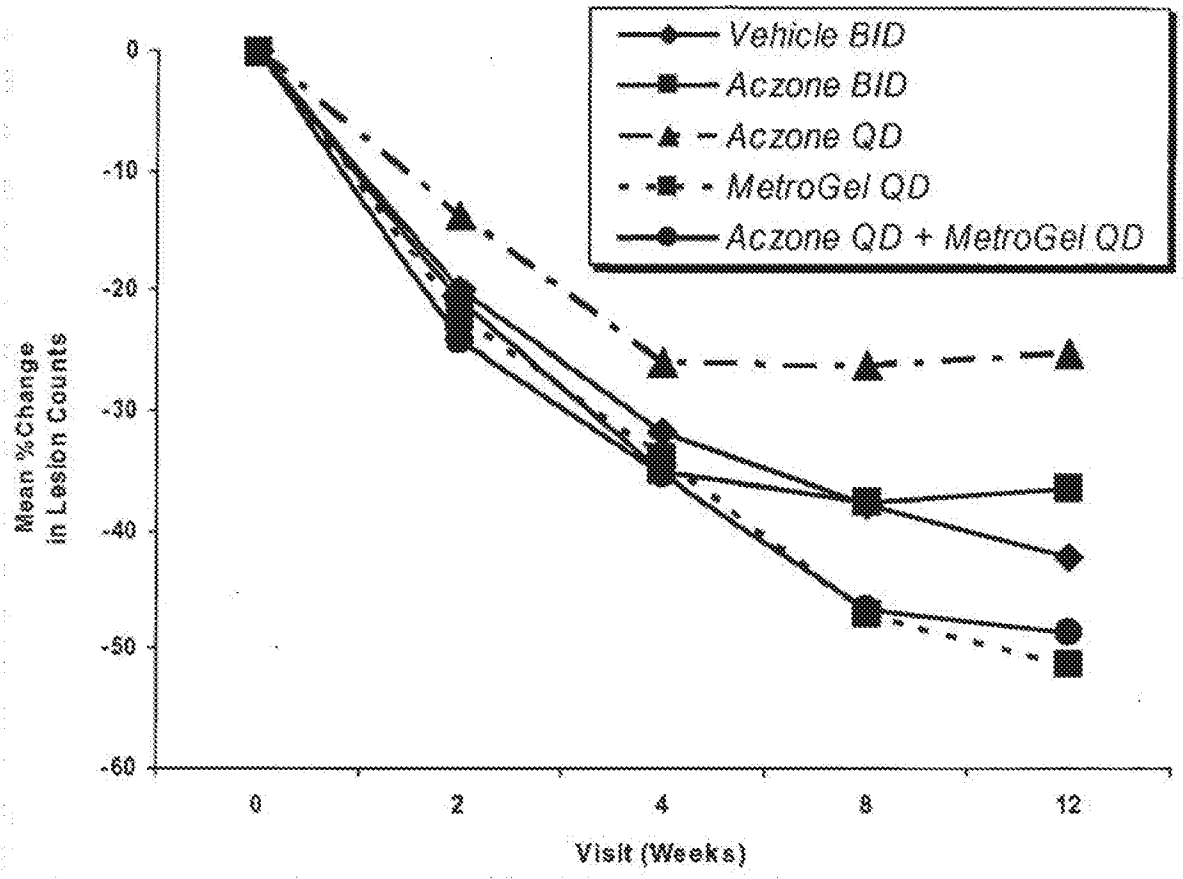
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 2

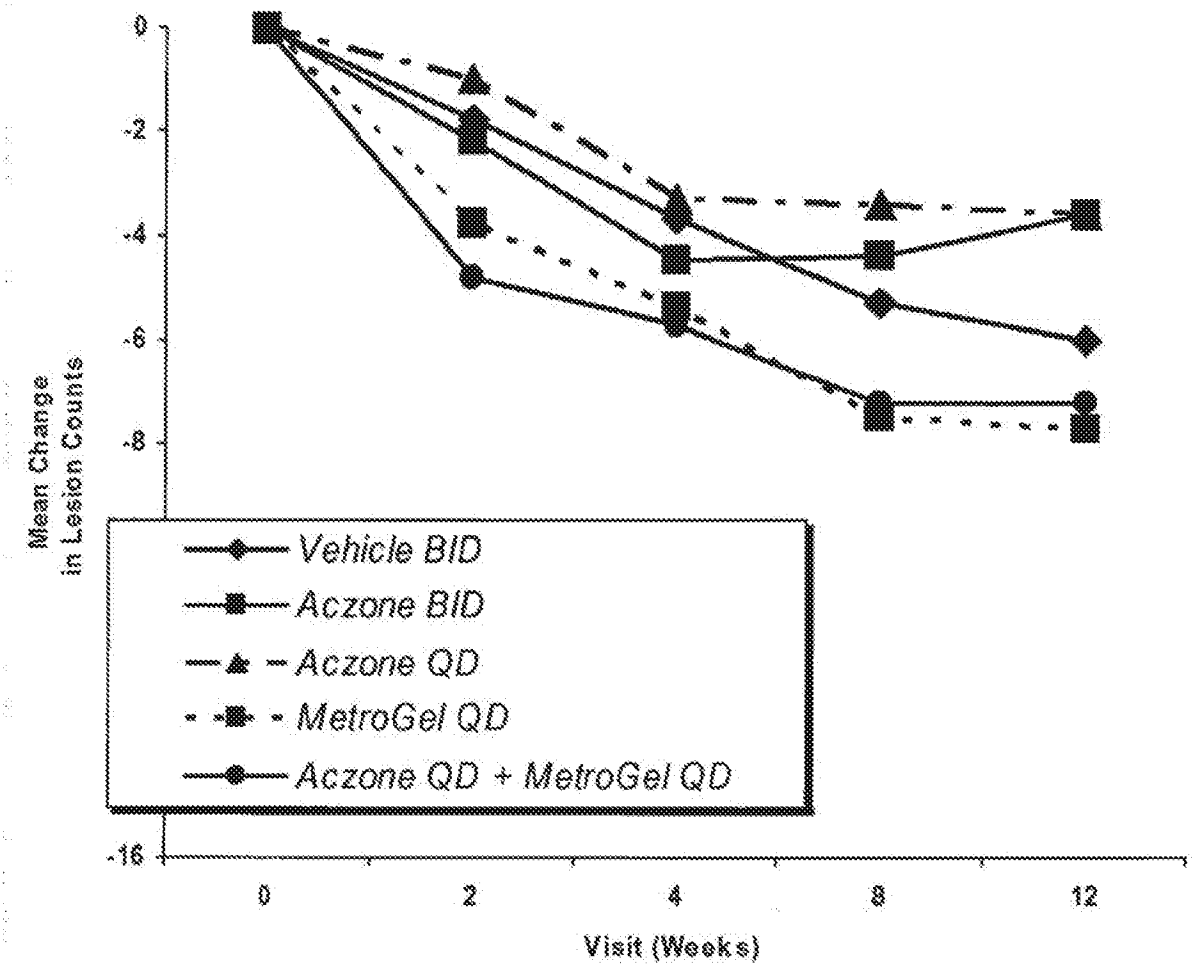
0
-2
-4
-6
-8
-16
Mean Change in Lesion Counts
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
0
2
4
8
12
Visit (Weeks)

FIG. 3

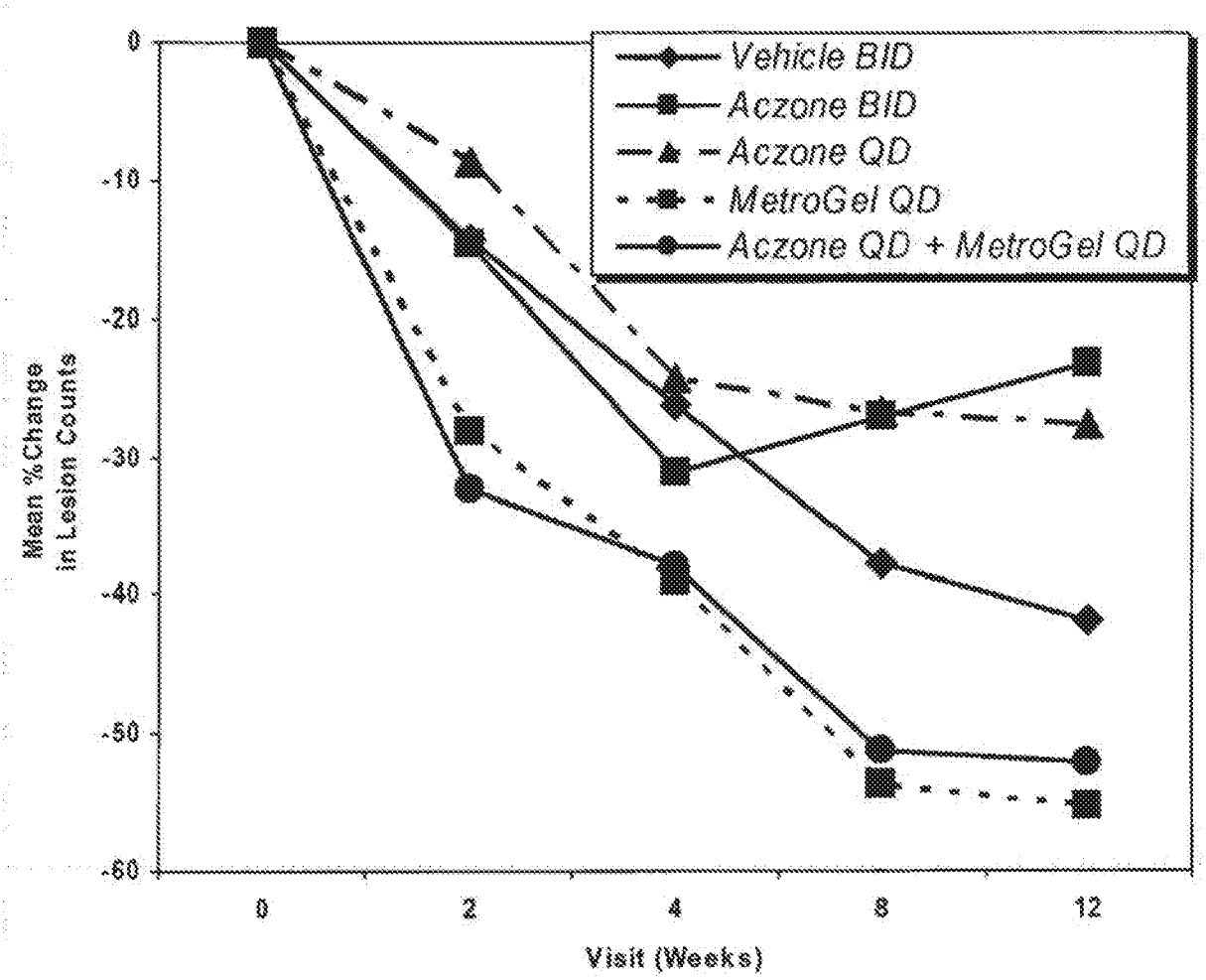
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 4

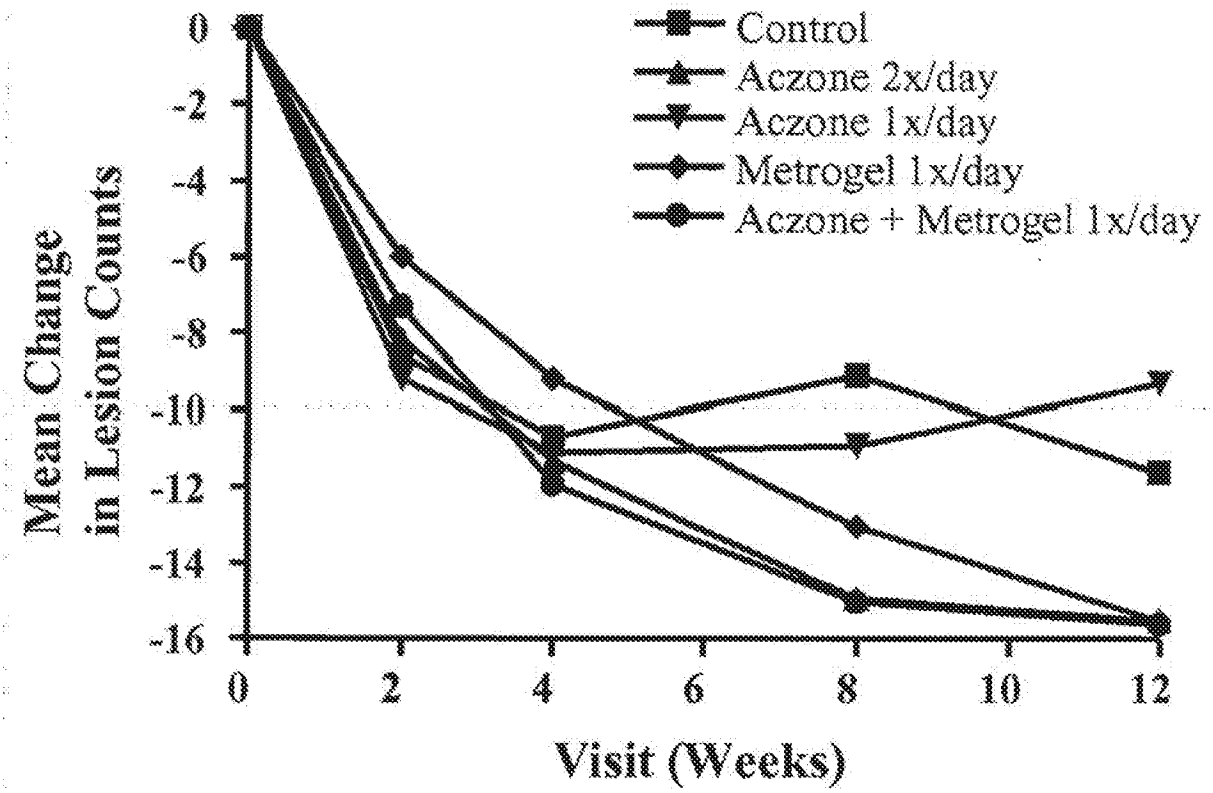
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
-14
-16
0
2
4
6
8
10
12
Visit (Weeks)

FIG. 5

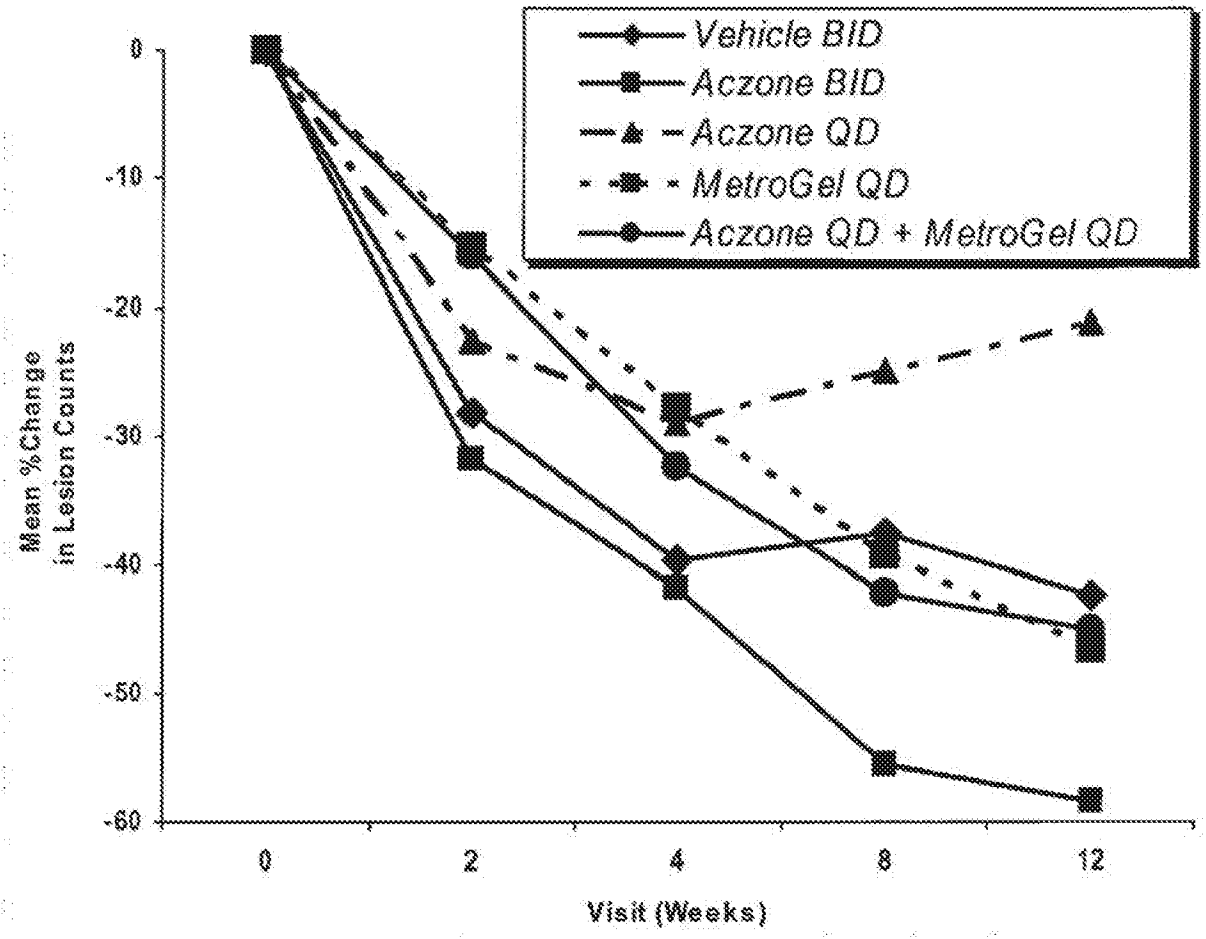
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean %Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 6

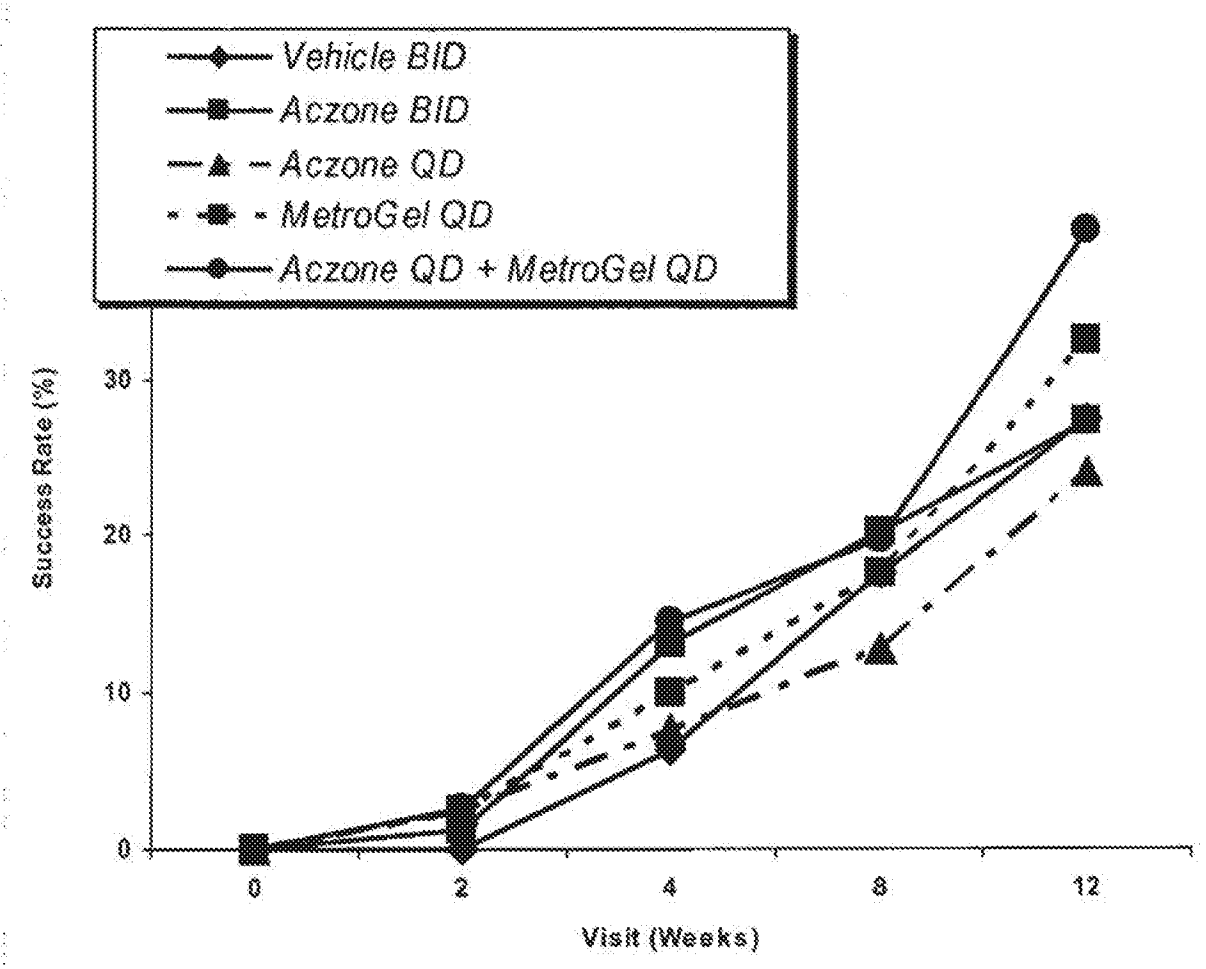
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Success Rate (%)
0
10
20
30
0
2
4
8
12
Visit (Weeks)

FIG. 7

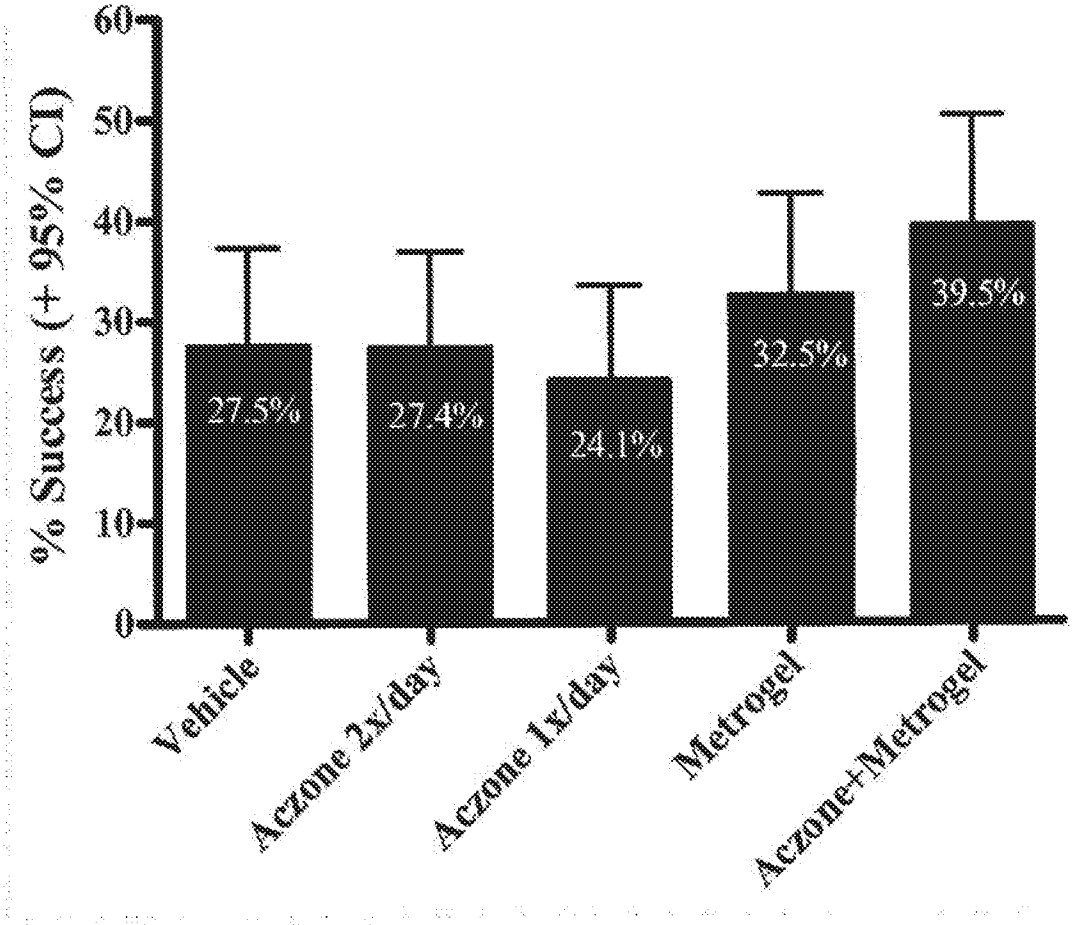
% Success (+ 95% CI)
60
50
40
30
20
10
0
27.5%
27.4%
24.1%
32.5%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

FIG. 8

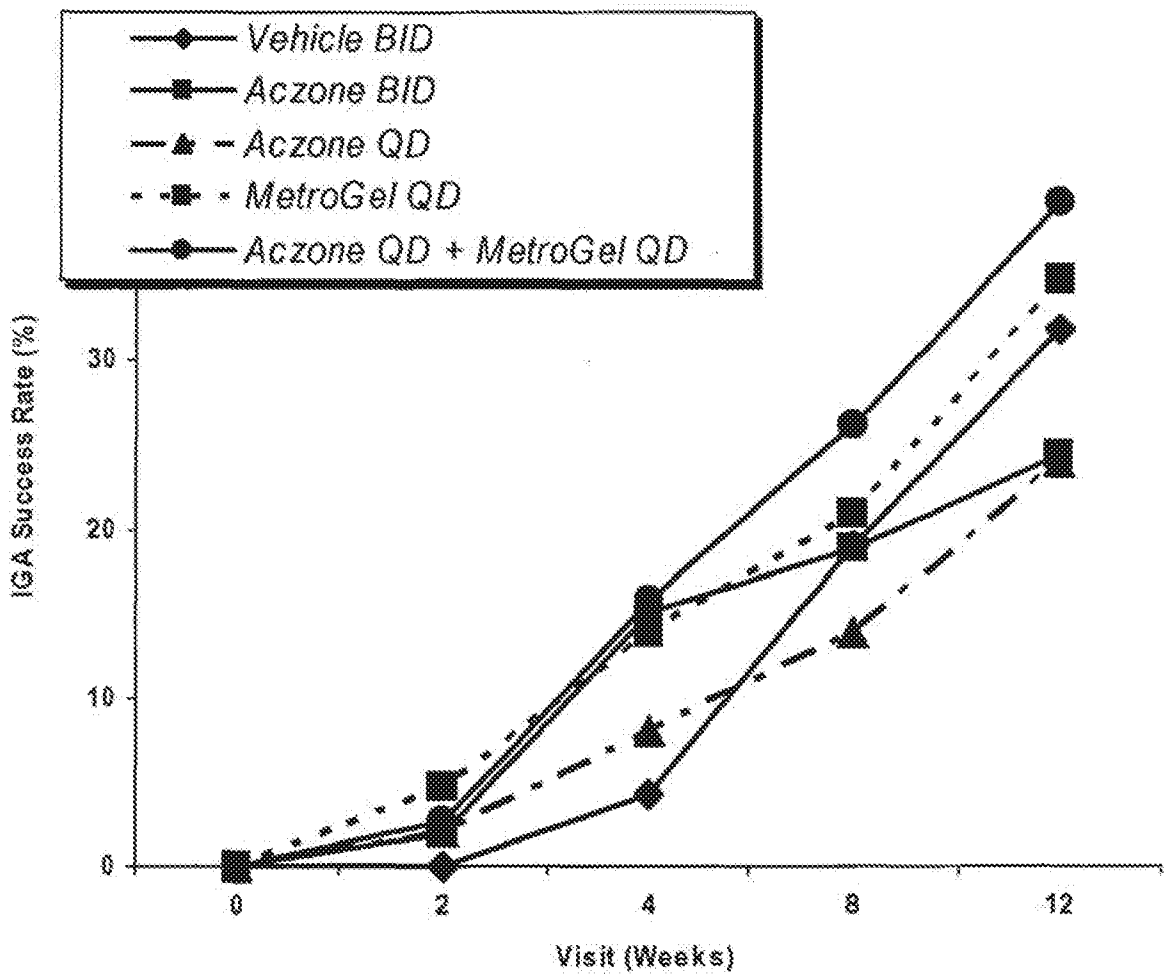
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
0
10
20
30
0
2
4
8
12
Visit (Weeks)

FIG. 9

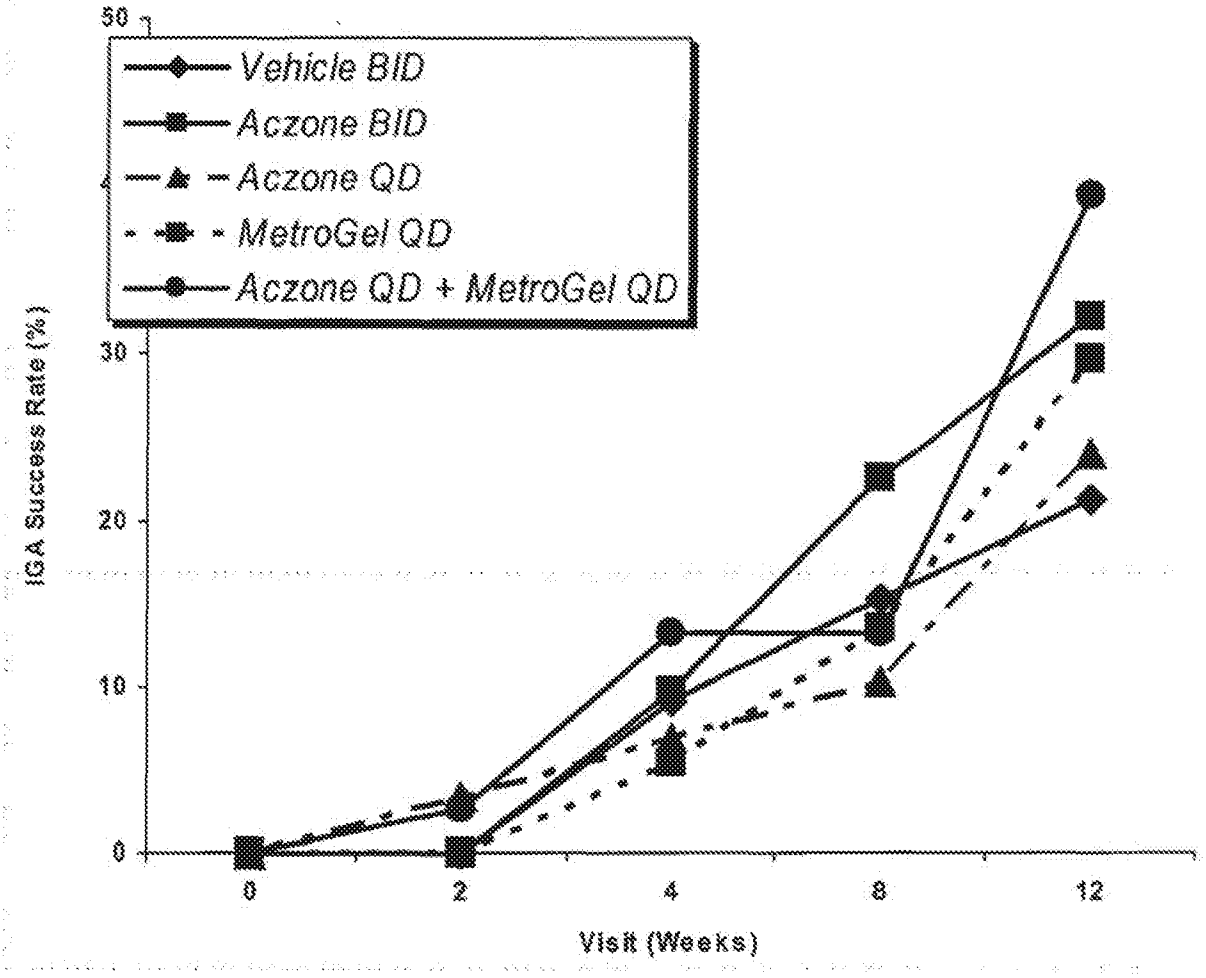
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
50
30
20
10
0
0
2
4
8
12
Visit (Weeks)

FIG. 10

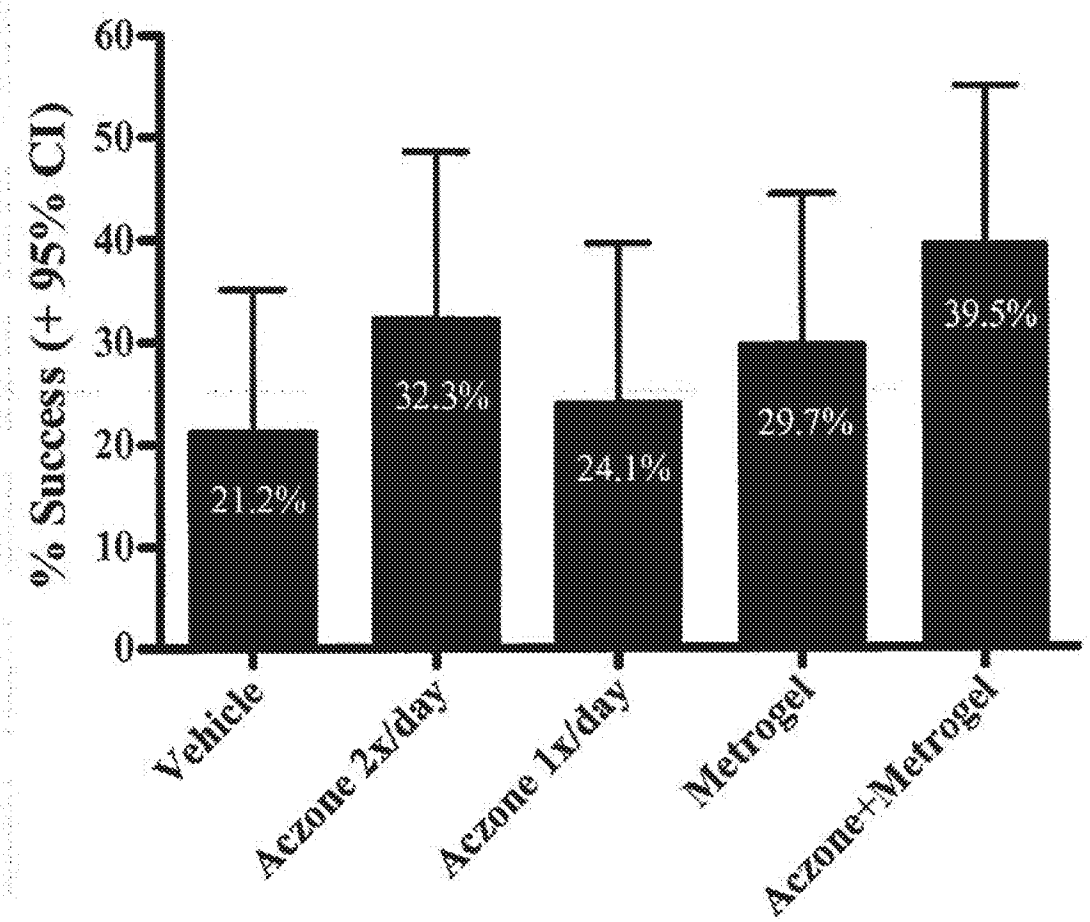
% Success (+ 95% CI)
60
50
40
30
20
10
0
21.2%
32.3%
24.1%
29.7%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/02549

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 8/02 (2008.04)
USPC - 424/401, 514/170, 174, 646 - search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (USPT, PGPB, EPAB, JPAB), Google Scholar, WIPO, PubMed

Search terms - Dapsone, acne, rosacea, metronidazole, topical, papulopustular, ocular

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0122435 A1 (OSBORNE) 31 May 2007 (31.05.2007), esp para [0013], [0034], [0001]	1-89 and 91-96
Y	"UPDATE ON THE TREATMENT OF ROSACEA, A BASIC GUIDE TO CURRENT APPROACHES.", John Wolf, PRESENTATIONS FROM THE WINTER CLINICAL DERMATOLOGY CONFERENCE HELD IN MAUI, HAWAII, JANUARY 13 -17, 2006. From: http://www.skinandaging.com/supplements/pdf/wcd_1106.pdf retrived on 22 May 2008	1-89 and 98-99
X — Y	US 2007/0281984 A1 (DOLFI et al) 06 December 2007 (06.12.2007), esp para [0010],[0037], [0036]	90 ——— 2-10, 20-22, 25-33, 43-45, 48-49, 51-52, 55-56, 58-64, 66-73, 75-82, 85-89 and 91-96
Y	"Two Randomized Studies Demonstrate the Efficacy and Safety of Dapsone gel, 5% for the Treatment of Acne vulgaris" Z. Draelos, et al. J Am Acad Dermatology March 2007 Vol 56, No 3, pages 439, e1 - 439 e10.esp Table II, Figure 3, Figure 3c	4-9,28-33,55-56,59-64,67-70,72-73,75-78,81-82,85-89 and 91-96
X — Y	WO 2005/016296 A1 (LATHROP et al) 24 February 2005 (25.02.2005), esp (page 1, ln 25-28), and (page 1, ln 25-28)	97,100 ——— 98-99

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 2008 (15.05.2008)	11 JUN 2008

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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A61K 31/192 (2006.01)

(21) International Application Number:
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29 July 2010 (29.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(72) Inventors; and

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(74) Agents: **WURST, John** et al.; Allergan, Inc., 2525 Dupont Drive, Irvine, California 92612 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: COMBINATION OF DAPSONE WITH ADAPALENE

Fig. 1

Ingredient	Composition (% w/w)						
	1	2	2.1-5	3	4	4.1-5	5
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	25.0	5-15	5-15	15.0	-	-	-
Lactic Acid	2.0	-	-	-	-	-	-
Dimethyl Isosorbide	-	5-15	5-15	-	5-15	5-15	-
Propylene Glycol	-	-	-	10.0	10.0	10.0	-
Glycerin	-	-	-	2.0	2.0	3.0	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	-
Citric Acid	0.05	0.05	0.05	0.05	0.05	0.05	-
HEC	1-4	1-4	-	-	1-4	-	-
Carbopol 980	-	-	0.5-2	0.75	-	0.5-2	0.95
NaOH or Tromethine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	0.2 (NaOH)
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Methylparaben	-	-	-	-	-	-	0.2
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

(57) Abstract: A composition suitable for topical application that contains at least two active ingredients, one of these being dapsone and one selected from the group consisting of adapalene, tazarotene and tretinoin for the effective treatment of acne and other dermatological conditions.

WO 2011/014627 A1

COMBINATION OF DAPSONE WITH ADAPALENE

Cross Reference

This application claims the benefit of U.S. Provisional Patent Application Serial Number 61/229,903 filed on July 30, 2009, the entire disclosure of which is incorporated herein by this specific reference.

Field of the Invention

The present invention is directed to compositions and methods for the treatment of acne vulgaris and other dermatological conditions.

Background of the Invention

Acne is the most common skin disease that affects a large number of adolescents and young adults after they reach puberty. Though not a life threatening disease, it has serious psychological impact on the patient. Chronic inflammatory acne can also result in permanent scarring of the face.

There are multiple factors that contribute to the pathogenesis of acne, these include: 1. over activity of sebum production as a result of hormonal changes at puberty; 2. colonization of *Propionibacterium acnes* (*P.acnes*) in the pilosebaceous unit; 3. hyperkeratinization or abnormal desquamation of epithelium of the upper follicle (above the sebaceous gland) that results in blockage of the pilosebaceous canal; 4. formation of inflammatory molecules as a result of the action of *P.acnes* on sebaceous lipids.

The obstruction of the pilosebaceous canal and inflammation caused by *P.acnes* created inflammatory metabolites results in the formation of comedones. Excess sebum production as a result of hormonal changes at puberty, combined with increased epithelium turnover of the upper follicle leads to formation of microcomedones which progresses to inflammatory papules and pustules in acne. The combination of lipid rich sebum and protein rich desquamated cells provides an ideal environment for the growth and activity of *P.acnes* which converts the sebaceous lipids to the inflammatory free fatty acid molecules resulting in inflammatory acne lesions. The patient can have either non-

inflammatory (open and closed comedones), inflammatory (papules and pustules) or a combination of both which most often is the case. Topical treatments are generally sufficient in most patients to control the acne lesions.

Because acne is a multifactorial condition, the marketed products work on one or more of the underlying factors contributing to acne for its treatment. There are number of prescription and over-the-counter (OTC) products available that treat acne; however, they all lack either desired efficacy or tolerability or both. Currently available products include antibiotics (topical and systemic), benzoyl peroxide, retinoids (topical and systemic), dapsone, and a number of other compounds.

The anti-acne molecule dapsone is marketed as a commercial product Aczone®. Aczone® is a 5% dapsone gel with a gritty texture due to insoluble particles of dapsone drugs. The insolubility of dapsone limits the bioavilability of dapsone upon application and its absorption through the skin and is therefore administered twice daily. At the biochemical and molecular level, dapsone exhibits an anti-inflammatory activity which provides a unique mechanism of action for this molecule in treatment of inflammatory acne lesions. However, its mechanism of action is not entirely understood. A complex combination of inflammatory pathways produce the clinical inflammation observed in acne. It is known that neutrophils significantly contribute to inflammatory acne. Dapsone is known to suppress neutrophil recruitment & local production of toxic products there by inhibiting neutrophil chemotaxis and reducing generation of oxygen free radicals. It further inhibits release of lysosomal enzymes and reduces release and bocks inflammatory effects of prostaglandins & leukotrienes. These effects results in reduction of inflammatory acne lesions. In addition to its anti-inflammatory activity, dapsone is also effective against *P. acnes*. MIC90 against *P. acnes* is 8μg/ml.

Adapalene is a third generation retinoid, which are compounds related to Vitamin A, and has been approved by the FDA for the treatment of acne. Adapalene is known to moderate inflammatory processes but its mechanism of action is also not entirely understood. Adapalene products are sold with the concentrations of 0.1% and 0.3% w/v concentrations for gels and 0.1% w/v concentration for cream. Adapalene acts on retinoid receptors and appears to be a modifier of cellular differentiation, keratinization and inflammatory processes which are involved in the pathology of *acne vulgaris*. Absorption of adapalene from either 0.1% or 0.3% gel or cream is low. In one pharmacokinetic study,

16 patients suffering from *acne vulgaris* received 0.3% adapalene gel applied to the face, chest and back which is approximately a dosage of 2 mg/cm2. Fifteen patients resulted in quantifiable (LOQ = 0.1 ng/mL) adapalene levels with a mean C_{max} of 0.553 ± 0.466 ng/mL on Day 10 of treatment. Mean $AUC_{0\text{-}24hr}$ was 8.37 ± 8.46 ng.h/mL as determined in 15 of the 16 patients on Day 10. Terminal apparent half-life, which was determined in 15 of 16 patients, ranged from 7 to 51 hours, with a mean of 17.2 ± 10.2 hours. Adapalene was rapidly cleared from plasma and was not detected 72 hours after the last application for all but one subject.

Summary of the Invention

There is an unmet consumer need for an efficacious product for the treatment of *acne vulgaris* as the currently available products for treatment of *acne vulgaris* lack the desired efficacy and/or have side effects or tolerability issues that are undesired by the subjects.

A combination acne product would provide the benefit of enhanced efficacy compared to the products containing single active agent by taking advantage of the synergistic mechanism of action of the active agents for treatment of acne. The present invention is directed to acne products with at least two active compounds and in particular are directed to dapsone and adapalene combination formulations for the use in the treatment of dermatological conditions such as *acne vulgaris*, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, psoriasis, cosmetic improvement of surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, eczema, and miliaria and other dermatological conditions.

Some embodiments of the present invention include:

1) A dermatological composition comprising dapsone, adapalene, and water.

2) The dermatological composition of paragraph 1 wherein the composition comprises 5% w/w dapsone and 0.1% or 0.3% w/w adapalene and is used for the treatment of *acne vulgaris*.

3) The dermatological composition of paragraph 2 wherein the composition is 0.5% w/w dapsone and 0.3% w/w adapalene.

4) The dermatological composition of paragraph 1 wherein the composition is a gel.

5) The compositions of paragraphs 1 and 4 wherein the composition is 0.5% w/w dapsone, 0.1% w/w adapalene, 1.5% w/w benzyl alcohol, transcutol, 5 – 25% w/w PEG 400, 0.01% w/w EDTA, and 0.03% w/w citric acid. ,

6) The compositions of paragraphs 1 - 5 wherein the composition further comprises hydroxyl ethyl cellulose 1 – 4% w/w.

7) The compositions of paragraphs 1 - 5 further comprising carbopol 980 at 0.5 – 2% w/w.

8) The compositions of paragraphs 1 – 7 further comprising methyl paraben.

9) The compositions of paragraphs 1 – 8 further comprising lactic acid.

10) The compositions of paragraphs 1 – 9 further comprising glycerin.

11) The composition of paragraph 5 further comprising dimethyl isosorbide in 5 – 15% w/w.

12) The composition of paragraphs 1 - 5 wherein transcutol is present in the amount of 25% w/w.

13) The compositions of paragraphs 1 – 12 wherein a buffer selected from the group consisting of NaOH, trolamine, and hycrochloric acid is added to adjust the pH.

14) The compositions of paragraphs 1 - 13 wherein the pH of the composition is 5.5.

15) The composition of paragraphs 1 - 5 further comprising 2 – 3 % hydroxyl ethyl cellulose.

16) The compositions of paragraphs 1 - 15 wherein the composition is in the form of one selected from the group consisting of a gel, emulsion, cream, liquid, paste, lotion, nanoemulsion, microemulsion, reverse emulsion and liposomal cream.

17) The compositions of paragraphs 1- 16 wherein the composition may be used for treatment of one selected from the group consisting of *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, and miliaria and other dermatological conditions.

18) A method of treating *acne vulgarus* by application of the compositions of paragraphs 1 - 17.

19) The method of treatment of paragraph 17, wherein the application is once a day.

20) The method of treatment of paragraph 17, wherein the application is twice a day.

Brief Description of the Drawings:

Fig. 1 is directed to dapsone and adapalene formulations for the treatment of dermatological conditions;

Fig. 2 is directed to variations of formulations for the treatment of dermatological conditions of Formula 1 of Figure 1;

Fig. 3A is directed to variations of formulations for the treatment of dermatological conditions of Formula 2 of Figure 1;

Fig. 3B is directed to variations of formulations for the treatment of dermatological conditions of Formula 2 of Figure 1;

Fig. 3C is directed to variations of formulations for the treatment of dermatological conditions of Formula 2.1 of Figure 1;

Fig. 3D is directed to variations of formulations for the treatment of dermatological conditions of Formula 2.1 of Figure 1;

Fig. 4A is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4B is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4C is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1;

Fig. 4D is directed to variations of formulations for the treatment of dermatological conditions of Formula 4 of Figure 1; and,

Fig. 5 is directed to dapsone and adapalene formulations for the treatment of dermatological conditions.

Detailed Description of the Invention

The present invention is directed to topical compositions for treatment of dermatological conditions which contain at least two active ingredients, one of these being dapsone and the other(s) selected from the list below for an effective treatment of acne and other dermatological conditions such as rosacea.

Some broad embodiments of the invention and possible combinations are found below:

Suitable compounds that can be combined with dapsone (2 – 10% w/w) include:

1. Agents with bactericidal and/or comedolytic properties:
    a. Benzoyl peroxide (2.5 – 10% w/w); and,

b. other antimicrobial actives that are effective against *P.acnes*.

2. Agents that inhibit comedogenesis by reducing pilosebaceous canal obstruction or have keratolytic properties such as:
   a. Salicylic acid (0.5 – 3% w/w);
   b. Azelaic acid (up to 20% w/w);
   c. Sulfacetamide-sulfur (5 – 10% w/w); and,
   d. other keratolytic agents.
3. Agents that reduce sebaceous gland secretion and effect epithelial dysquamation:
   a. Retinoids:
      i. tretinoin or trans retinoic acid (0.02 – 0.1% w/w);
      ii. Tazarotene (0.05 – 0.1% w/w);
      iii. Adapalene (0.1 – 0.3% w/w); and,
      iv. additional retinoids.
4. Topical antibiotics for directly killing *P. acnes*:
   a. erythromycin (1 – 3% w/w);
   b. clindamycin (1 – 2% w/w); and,
   c. tetracycline (1 – 3% w/w).

Potential combinations that can be used:

1. Dapsone (0.01% - 10% w/w) + retinoid (0.001% - 3% w/w)
   Examples:
   a. Dapsone 5% w/w + Adapalene 0.3% w/w;
   b. Dapsone 5% w/w + tazarotene 0.1% w/w; and,
   c. Dapsone 5% w/w + tretinoin 0.1% w/w.
2. Dapsone + benzoyl peroxide:
   Examples:
   a. Dapsone 5% w/w + benzoyl peroxide 5% w/w;
3. Dapsone + antibiotic:
   Examples:
   a. Dapsone 5% w/w + clindamycin 1% w/w.
4. Dapsone + keratolytic agent
   Examples:
   a. Dapsone 5% w/w + Azelaic acid 20% w/w.

The concentration values (w/w) in parenthesis represent preferred concentration; however, other concentrations values (w/v) can be used dependent on the formulation characteristics and the desired level of efficacy and tolerability.

In a recent clinical trial the safety and efficacy of dapsone gel co-administered with adapalene gel was assessed. The study design consisted of having patients apply the product Aczone® (5% w/w dapsone) twice a day, with morning and evening application. About 10 minutes after the evening application of Aczone®, patients applied a thin layer of 0.1 % w/w adapalene gel. The 10 minute separation between applications of the two products ensured complete absorption of the Aczone® formulation into the skin to minimize the potential negative impact on adapalene or dapsone skin penetration. Application of the 0.1% w/w adapalene gel immediately after the Aczone® application may have resulted in a situation where the adapalene or dapsone would have a lower skin penetration because of the mixing of the two formulation vehicles. Further, the additional thickness of the combined formulation applications may increase the penetration distance of the two actives also resulting in reduced skin penetration of the actives.

The results of the trial showed that dapsone gel administered concurrently (but not together) with adapalene gel is safe and well tolerated for the treatment of *acne vulgaris*. One aspect of the present invention is a combination adapalene/dapsone topical formulation combining the two actives into one formulation. The novelty of this invention is in part attributable to the use of additional excipients (solubilizers) in combination with diethylene glycol monoethyl ether ("DGME") in order to solubilize dapsone. Addition of cosolvents has enabled the complete dissolution of dapsone in the formulation and an increase in the solubility of adapalene (adapalene is not completely solubilized in these formulations). The increased concentration of dissolved dapsone and adapalene versus the marketed product comparators administered concurrently will increase the rate of skin penetration of both drugs into and through the skin

Topical dosage forms of the present invention include, but are not limited to solutions, gels, creams, ointments, foams, emulsions, films, and facial/skin peels. The present invention is directed to topical dapsone and adapalene formulations which are formulated to optimize the dermal delivery profile of adapalene and dapsone to effectively treat acne and other dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin.

Examples of some formulations encompassed by the present invention excipients and concentration ranges are summarized in Table 1 below:

Table 1: Example Excipient Composition Ranges Utilized in Adapalene / Dapsone Topical Formulations:

Ingredient	Function	Composition (% w/w)
Dapsone	Active	0.5 - 10
Adapalene	Active	0.1-0.3
Carbomer 980	Thickener	0.05 – 1.5
Hydroxyethyl cellulose		1-8%
Hydroxypropyl cellulose		1-6%
NaOH	Neutralizing Agent	0.01 – 2.0
Trolamine	Neutralizing Agent	0.01 – 2.0
Ethanol	Solubilizers	1 – 90
Lactic acid		1- 10
diethylene glycol monoethyl ether		1 – 50
propylene glycol		1 – 60
Dimethyl isosorbide		1 -30
Polyethylene glycol 400		1 – 50
Hexylene glycol		1 – 50
Isostearyl alcohol		0.5 – 10
Medium chain triglycerides		0.5 – 10
Isopropyl myristate		2 – 10
Benzyl alcohol	Preservative	0.5-5
Methyl Paraben	Preservative	0.1-0.3
Propyl Paraben	Preservative	0.01-1
Benzalkonium Chloride	Preservative	0.1-0.2
Sorbic Acid	Preservative	0.1-2.7
Glycerol	Humectant	1 – 20
Polyvinyl alcohol	Film forming	1-30
Water	Vehicle	1 - 90
EDTA Disodium	Antioxidant	0.005 – 0.02
Citric Acid	Antioxidant	0.015 – 0.06
Butylated hydroxytoluene	Antioxidant	0.005 – 1
Butylated hydroxyanisole	Antioxidant	0.01 -0.25
Propyl gallate	Antioxidant	0.01 – 0.1
Elastomer 10	Thickener	0.1-90
ST Wax 30	Thickener	0.1-50
Dimethiconol blend 20	Thickener	0.1-50
Emulsifier 10	Emulsifier	0.1-50
cyclomethicone 5	Solvent	0.1-50
Silicone fluid	Solvent	0.1-50
Silky wax 10	Thickener	0.1-50

Further specific compositions of the present invention of 5% w/w dapsone and 0.1% w/w and 0.3% w/w adapalene formulations include but are not limited to:

Table 2A: Adapalene / Dapsone Topical Formulations

Ingredient	Function	Composition (% w/w)								
Dapsone	Active	5	5	5	5	5	5	5	5	5
Adapalene	Active	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%	0.1% or 0.3%
diethylene glycol monoethyl ether	Solubilizing Agent	25	20	25	20	25	25	25	25	25
Benzyl Alcohol	Preservative	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	Solubilizing Agent	25	20	25	20	15	-	-	-	-
Lactic Acid	Solubilizing Agent	5	4	-	-	-	-	-	-	-
Dimethyl Isosorbide	Solubilizing Agent	-	-	-	-	15	-	-	-	-
Propylene Glycol	Solubilizing Agent	-	-	-	-	-	20	20	10	-
Glycerin	Humectant	-	-	-	-	-	10	10	2	-
Isopropyl Myristate	Solubilizing Agent	-	-	-	-	-	-	-	-	5
EDTA	Antioxidant	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	-

Disodium											
Citric Acid	Antioxidant	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	-
Hydroxyethyl Cellulose	Thickener	4	3		-	4	-	-	-	-	-
Carbopol 980	Thickener	-	-	-	0.75	-	0.75	0.75	0.75	0.75	-
Hydroxypropyl Cellulose	Thickener	-	-	-	-	-	-	-	-	-	3
NaOH	Neutralizing Agent	1.5	1.2	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Diluted Hydrochloric Acid	Neutralizing Agent	-	-	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Ethanol	Solubilizer	-	-	-	-	-	-	-	-	-	60
Water	Vehicle	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	-

Table 2B, Adapalene / Dapsone Topical Formulations (cont.)

Ingredient	Function	Composition (% w/w)		
Dapsone	Active	5	5	5
Adapalene	Active	0.1% or 0.3%	0.1% or 0.3%	0.1%5 or 0.3%
diethylene glycol monoethyl ether	Solubilizing Agent	25	25	25 10
Benzyl Alcohol	Preservative	1.5	1.5	1.5
PEG 400	Solubilizing Agent	13	-	- 15
Dimethyl Isosorbide	Solubilizing Agent	-	13	13
Propylene Glycol	Solubilizing Agent	15	15	1320
Glycerin	Humectant	2	2	2
EDTA Disodium	Antioxidant	0.01	0.01	0.01
Citric Acid	Antioxidant	0.03	0.03	0.03
Hydroxyethyl Cellulose	Thickener	-	2	-
Carbopol 980	Thickener	0.75	-	-
Hydroxypropyl Cellulose	Thickener	-	-	2
NaOH	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. 30 pH 5.5
Diluted Hydrochloric Acid	Neutralizing Agent	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Water	Vehicle	q.s.a.d.	q.s.a.d.	q.s.a.d.

The formulations of the present invention can be made as follows based on the excipients:

Process for making lactic acid containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, lactic acid, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;

b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;

c. Add adapalene to mixture in step b;

d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making DMI / hydroxyethyl cellulose containing formulations:
The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, dimethyl isosorbide, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved.
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making DMI / Carbopol containing formulations:
The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, dimethyl isosorbide, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/PEG containing formulations:
The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, polyethylene glycol 400, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/DMI/Carbopol containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, dimethyl isosorbide, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add Carbopol 980 to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,
e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

Process for making PG/DMI/HEC containing formulations:

The combination adapalene/dapsone gels were prepared as follows:

a. Weigh the Transcutol into a kettle. Add the dapsone, propylene glycol, dimethyl isosorbide, benzyl alcohol. Stir with propeller mixer at room temperature. Mix until dissolved;
b. Add water, EDTA, and citric acid to mixture in step a. Mix until dissolved;
c. Add adapalene to mixture in step b;
d. While continuing to mix, slowly add hydroxyethyl cellulose to mixture in step c avoid clumping. Mix vigorously at room temperature until a uniform lump-free dispersion is achieved; and,

e. While mixing add sufficient sodium hydroxide to achieve a pH of 5.3 to 5.7. Mix until uniform.

The most effective dapsone and adapalene composition is selected based on clinical studies. For example, a clinical study is conducted by forming two treatment groups, one with daily application of a selected dapsone and adapalene formulation, and twice daily topical application of the same selected dapsone and adapalene formulation to the acne area of the skin for a period of 12 weeks. Two control groups are formed with application once and twice daily of a vehicle consisting of the same excipients but no active ingredients. The patient's inflammatory and non-inflammatory acne lesion counts should be recorded at baseline before initiation of treatment and then at select intervals throughout the study. The reduction in total, non-inflammatory or inflammatory lesions counts provides determination of the efficacy of the formulations. The established Global Acne Assessment Score (GAAS) should be used to assess efficacy of the product. The tolerability of the product can be determined by assessment of skin dryness, irritation, sensitivity and redness as a result of treatment. A product is considered to have better tolerability if there is less effect on these parameters.

Application method:

1. A suitable application method is topical cream, gel, lotion, ointment, foam, liquid or a semi solid preparation. A topical preparation may contain additional ingredients to provide aesthetic and moisturizing and anti-inflammatory benefits to the skin. Generally,
    a. A gel or liquid preparation can be alcohol or aqueous based or a combination of two;
    b. A nanoemulsion or microemulsion preparation can be used for enhanced delivery of actives;
    c. A liposomal cream or lotion preparation can be used for enhanced delivery of actives; and
    d. A foam preparation can be a quick breaking foam with additional emollient components.
2. Topical preparations that result in slow release or controlled release of the active agent can also be used to provide an optimal efficacy and tolerability balance.

3. Active ingredients encapsulated in micro beads or adsorbed on microsponge can be used for control release and in addition solve any incompatibility issues between the formulation ingredients.
4. The application is preferably once a day or more frequent depending on the desired effect.

Application of the formulations of the present invention:

Example #1 – Application of 0.1% w/w adapalene of Formula 1 in Fig. 5

A 17 year old Caucasian male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #1 in Fig. 5. The 17 year old male patient applies the 0.1% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 17 year old male patient experiences a 32% reduction in inflammatory and non-inflammatory lesions.

Example #2 - Application of 0.3 % w/w adapalene of Formula 1 in Fig. 5

A 16 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #1 in Fig. 5. The 16 year old female patient applies the 0.3% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 16 year old female patient experiences a 41% reduction in inflammatory and non-inflammatory lesions.

Example #3 – Application of 0.1% w/w adapalene of Formula 2 in Fig. 5

A 23 year old African-American female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #2 in Fig. 5. The 23 year old female patient applies the 0.1% w/w adapalene composition of Formula 2 once daily for 12 weeks. After 12 weeks, the 23 year old female patient experiences a 24 % reduction in inflammatory and non-inflammatory lesions.

Example #4 – Application of 0.3% w/w adapalene of Formula 2 in Fig. 5

A 19 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #2 in Fig. 5. The 19 year old female patient

applies the 0.3% w/w adapalene composition of Formula 2 once daily for 12 weeks. After 12 weeks, the patient experiences a 248 % reduction in inflammatory and non-inflammatory lesions.

Example #5 – Application of 0.1% w/w adapalene of Formula 3 in Fig. 5

A n 18 year old African-American male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #3 in Fig. 5. The 18 year old male patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the 18 year old male patient experiences a 29 % reduction in inflammatory and non-inflammatory lesions.

Example #6 – Application of 0.3% w/w adapalene of Formula 3 in Fig. 5

A n 23 year old Asian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #3 in Fig. 5. The 23 year old patient applies the 0.3% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the patient experiences a 25 % reduction in inflammatory and non-inflammatory lesions.

Example #7 – Application of 0.1% w/w adapalene of Formula 4 in Fig. 5

An 18 year old African-American male patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #3 in Fig. 5. The 18 year old male patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the 18 year old male patient experiences a 29 % reduction in inflammatory and non-inflammatory lesions.

Example #8 – Application of 0.3% w/w adapalene of Formula 4 in Fig. 5

A 17 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #4 in Fig. 5. The 17 year old male patient applies the 0.3% w/w adapalene composition twice daily for 12 weeks. After 12 weeks, the 17 year old male patient experiences a 41 % reduction in inflammatory and non-inflammatory lesions.

Example #9 – Application of 0.1% w/w adapalene of Formula 5 in Fig. 5

A 16 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.1% w/w adapalene formulation according to formulation #5 in Fig. 5. The 16 year old female patient applies the 0.1% w/w adapalene composition once daily for 12 weeks. After 12 weeks, the patient experiences a 27 % reduction in inflammatory and non-inflammatory lesions.

Example #10 - Example #9 – Application of 0.3% w/w adapalene of Formula 5 in Fig. 5

A 19 year old Caucasian female patient suffers *acne vulgaris with* a combination of inflammatory and non-inflammatory lesions and applies a 0.3% w/w adapalene formulation according to formulation #5 in Fig. 5. The 19 year old female patient applies the 0.3% w/w adapalene composition twice daily for 12 weeks. After 12 weeks, the patient experiences a 38 % reduction in inflammatory and non-inflammatory lesions.

Example #11 – Application of 0.1% w/w adapalene of Formula 1 in Fig. 5

A 37 year old Caucasian male patient suffers from rosacea and applies a 0.1% w/w adapalene formulation according to formulation #1 in Fig. 5. The 37 year old male patient applies the 0.1% w/w adapalene composition of Formula 1 once daily for 12 weeks. After 12 weeks, the 37 year old male patient experiences a reduction in the symptoms of rosacea.

Claims:

1) A dermatological composition comprising dapsone, adapalene, and water.

2) The dermatological composition of claim 1 wherein the l composition comprises 5% w/w dapsone and 0.1% w/w adapalene and is used for the treatment of *acne vulgaris*. .

3) The dermatological composition of claim 2 wherein the composition is 0.5% w/w dapsone and 0.3% w/w adapalene.

4) The dermatological composition of claim 1 wherein the composition is a gel.

5) The composition of claim 1 wherein the composition is 0.5% w/w dapsone, 0.1% w/w adapalene, 1.5% w/w benzyl alcohol, transcutol, 5 – 25% w/w PEG 400, 0.01% w/w EDTA and 0.03% w/w citric acid. .

6) The composition of claim 5 wherein the composition further comprises hydroxyl ethyl cellulose 1 – 4% w/w.

7) The composition of claim 5 further comprising carbopol 980 at 0.5 – 2% w/w.

8) The composition of claim 5 further comprising methyl paraben.

9) The composition of claim 5 further comprising lactic acid.

10) The composition of claim 5 further comprising glycerin.

11) The composition of claim 5 further comprising dimethyl isosorbide at 5 – 15% w/w.

12) The composition of claim 5 wherein transcutol is present in the amount of 25% w/w.

13) The composition of claim 5 wherein a buffer selected from the group consisting of NaOH, trolamine, and hycrochloric acid is added to adjust the pH.

14) The composition of claim 13 wherein the pH of the composition is 5.5.

15) The composition of claim 5 further comprising 2 – 3 % hydroxyl ethyl cellulose.

16) The composition of claim 1 wherein the composition is in the form of one selected from the group consisting of a gel, emulsion, cream, liquid, paste, lotion, nanoemulsion, microemulsion, reverse emulsion and liposomal cream.

17) The composition of claim 5 wherein the composition may be used for treatment of one condition selected from the group consisting of *acne vulgaris,* rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis piralis, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, pruritis, lichen planus, nodular prurigo, dermatitis, eczema, and miliaria and other dermatological conditions.

18) A method of treating *acne vulgarus* by application of the composition of claim 1.

19) The method of treatment of claim 17, wherein the application is once a day.

20) The method of treatment of claim 17, wherein the application is twice a day.

Fig. 1

Ingredient	Composition (% w/w)						
	1	2	2.1-a	3	4	4.1-a	5
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	-
PEG 400	25.0	5-15	5-15	13.0	-	-	-
Lactic Acid	2.0	-	-	-	-	-	-
Dimethyl Isosorbide	-	5-15	5-15	-	5-13	5-13	-
Propylene Glycol	-	-	-	10.0	10.0	10.0	-
Glycerin	-	-	-	2.0	2.0	2.0	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	-
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	-
HEC	1-4	1-4	-	-	1-2	-	-
Carbopol 980	-	-	0.5-2	0.75	-	0.5-2	0.85
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	0.2 (NaOH)
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	-
Methylparaben	-	-	-	-	-	-	0.2
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

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Fig. 2

Ingredient	Composition (% w/w)						
	1	1-a	1-b	1-c	1-d	1-e	1-f
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Lactic Acid	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Dimethyl Isosorbide	-	-	-	-	-	-	-
Propylene Glycol	-	-	-	-	-	-	-
Glycerin	-	-	-	-	-	-	-
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	1	1.5	2	2.5	3	3.5	4
Carbopol 980	-	-	-	-	-	-	-
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

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Fig. 3A

Ingredient	Composition (% w/w)						
	2	2-a	2-b	2-c	2-d	2-e	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	10	15	5	10	15	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	1	1	1	2	2	2	
Carbopol 980	-	-	-	-	-	-	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 3B

Ingredient	Composition (% w/w)						
	2-f	2-g	2-h	2-i	2-j	2-k	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	10	15	5	10	15	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	3	3	3	4	4	4	
Carbopol 980	-	-	-	-	-	-	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

Fig. 3C

Ingredient	Composition (% w/w)						
	2.1-a	2.1-b	2.1-c	2.1-d	2.1-e	2.1-f	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	5	5	5	5	5	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	-	-	-	-	-	-	
Carbopol 980	0.5	0.5	0.5	1	1	1	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

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Fig. 3D

Ingredient	Composition (% w/w)						
	2.1-g	2.1-h	2.1-i	2.1-j	2.1-k	2.1-l	
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	
PEG 400	15	10	5	15	10	5	
Lactic Acid	-	-	-	-	-	-	
Dimethyl Isosorbide	5	5	5	5	5	5	
Propylene Glycol	-	-	-	-	-	-	
Glycerin	-	-	-	-	-	-	
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	
HEC	-	-	-	-	-	-	
Carbopol 980	1.5	1.5	1.5	2	2	2	
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	
Methylparaben	-	-	-	-	-	-	
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	

400

Fig. 4A

Ingredient	Composition (% w/w)							
	4	4-a	4-b	4-c	4-d	4-e	4-f	4-g
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	8	10	13	5	8	10	13
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	1	1	1	1	1.5	1.5	1.5	1.5
Carbopol 980	-	-	-	-	-	-	-	-
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

401

Fig. 4B

Ingredient	Composition (% w/w)							
	4-h	4-i	4-j	4-k	4.1-a	4.1-b	4.1-c	4.1-d
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	8	10	13	5	6	7	8
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	2	2	2	2	-	-	-	-
Carbopol 980	-	-	-	-	0.5	0.5	0.5	0.5
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

402

403

Fig. 4C

Ingredient	Composition (% w/w)							
	4.1-e	4.1-f	4.1-g	4.1-h	4.1-i	4.1-j	4.1-k	4.1-l
Dapsone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3
Transcutol® P	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
Benzyl Alcohol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG 400	-	-	-	-	-	-	-	-
Lactic Acid	-	-	-	-	-	-	-	-
Dimethyl Isosorbide	5	6	7	8	5	6	7	8
Propylene Glycol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EDTA Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
HEC	-	-	-	-	-	-	-	-
Carbopol 980	1	1	1	1	1.5	1.5	1.5	1.5
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5
Methylparaben	-	-	-	-	-	-	-	-
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.

Fig. 4D

Ingredient	Composition (% w/w)							
	4.1-m	4.1-n	4.1-o	4.1-p				
Dapsone	5.0	5.0	5.0	5.0				
Adapalene	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3	0.1 and 0.3				
Transcutol® P	25.0	25.0	25.0	25.0				
Benzyl Alcohol	1.5	1.5	1.5	1.5				
PEG 400	-	-	-	-				
Lactic Acid	-	-	-	-				
Dimethyl Isosorbide	5	6	7	8				
Propylene Glycol	10.0	10.0	10.0	10.0				
Glycerin	2.0	2.0	2.0	2.0				
EDTA Disodium	0.01	0.01	0.01	0.01				
Citric Acid	0.03	0.03	0.03	0.03				
HEC	-	-	-	-				
Carbopol 980	2	2	2	2				
NaOH or Trolamine	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5				
Diluted Hydrochloric Acid	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5	q.s. pH 5.5				
Methylparaben	-	-	-	-				
Water	q.s.a.d.	q.s.a.d.	q.s.a.d.	q.s.a.d.				

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Fig. 5

Ingredient	Function	Composition (% w/w)								Aczone + adapalene
Formulation #		1		2		3		4		5
Dapsone	Active	5		5		5		5		5
Adapalene	Active	0.1% and 0.3%		0.1% and 0.3%		0.1% and 0.3%		0.1% and 0.3%		0.1% and 0.3%
transcutol	Solubilizing Agent	25		25		25		25		25
Benzyl Alcohol	Preservative	1.5		1.5		1.5		1.5		
PEG 400	Solubilizing Agent	25		15		13				
Lactic Acid	Solubilizing Agent	5		-						
Dimethyl Isosorbide	Solubilizing Agent	-		15				13		
Propylene Glycol	Solubilizing Agent	-		-		15		15		
Glycerin	Humectant	-		-		2		2		
EDTA Disodium	Antioxidant	0.01		0.01		0.01		0.01		
Citric Acid	Antioxidant	0.03		0.03		0.03		0.03		
Hydroxyethyl Cellulose	Thickener	4		4				2		
Carbopol 980	Thickener	-		-		0.75				0.85
NaOH	Neutralizing Agent	q.s. pH 5.5		q.s. pH 5.5		q.s. pH 5.5		q.s. pH 5.5		0.2
Diluted Hydrochloric Acid	Neutralizing Agent	q.s. pH 5.5		q.s. pH 5.5		q.s. pH 5.5		q.s. pH 5.5		
Methyl paraben	Preservative	-		-		-		-		0.2
Water	Vehicle	q.s.a.d.		q.s.a.d.		q.s.a.d.		q.s.a.d.		q.s.a.d.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/043671

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4%, or vehicle gel for the treatment of acne vulgaris: A randomized, double-blind study" JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, C.V. MOSBY, ST. LOUIS, MO, US, vol. 56, no. 2, 1 February 2007 (2007-02-01), page AB16, XP005936732 ISSN: 0190-9622 the whole document	1-20
Y	US 2007/122435 A1 (OSBORNE DAVID W [US]) 31 May 2007 (2007-05-31) page 1, left-hand column, paragraph 1 claims 27-31	1-20

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2010	04/11/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Young, Astrid

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/043671

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Anonymous: "Aczone (dapsone) Gel 5%" Internet Article 1 March 2009 (2009-03-01), XP002606246 Retrieved from the Internet: URL:http://www.allergan.com/assets/pdf/aczone_pi.pdf [retrieved on 2010-10-21] page 6, item 11	1-20
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Y	WO 2008/017914 A2 (AHUMADA AYALA FERNANDO [MX]) 14 February 2008 (2008-02-14) page 8	1-20
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Y,P	FLEISCHER ALAN B JR ET AL: "Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study." JOURNAL OF DRUGS IN DERMATOLOGY : JDD JAN 2010 LNKD- PUBMED:20120423, vol. 9, no. 1, January 2010 (2010-01), pages 33-40, XP009140328 ISSN: 1545-9616 the whole document	1-20

2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/043671

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2006048747 A1	11-05-2006	AU 2005300313 A1	11-05-2006
		BR PI0517640 A	14-10-2008
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		US 2009318371 A1	24-12-2009
US 2010029781 A1	04-02-2010	NONE	

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(54) Title: TOPICAL PERSONAL CARE AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

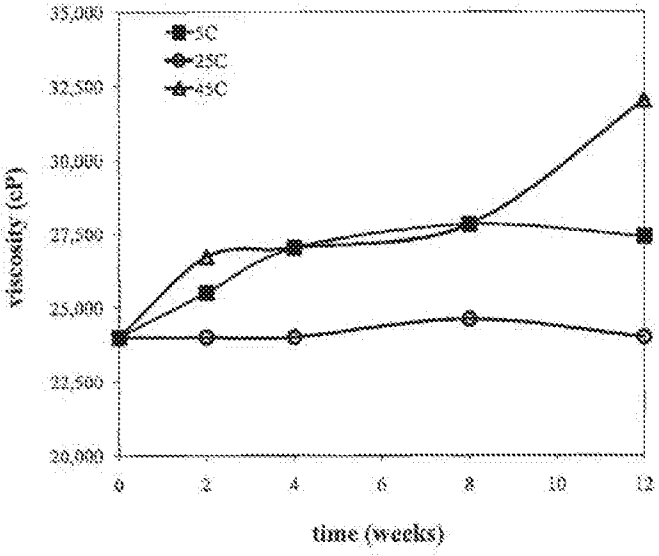

Fig. 1

(57) Abstract: Topical compositions are provided that have 0.5% or more of at least one personal care or pharmaceutical acid, and lightly- to moderately-crosslinked PVP, which is an effective thickener in the low pH systems. In preferred embodiments, the acid is a hydroxy acid and the composition used for personal care, or prescriptive or non-prescriptive medication indications for use on the skin, hair, scalp, foot, or lips. Also provided is the use of the topical compositions to deliver the acid(s) to the skin, hair, scalp, foot, or lips. Especially preferred is a use to reduce irritation and stinging compared to an equivalent compositions not having lightly- to moderately-crosslinked PVP.

WO 2010/105052 A1

TOPICAL PERSONAL CARE AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to topical compositions comprising at least one personal care acid or one pharmaceutical acid, and lightly- to moderately crosslinked poly(*N*-vinyl-2-pyrrolidone) ("PVP"). The lightly- to moderately crosslinked PVP has been found to provide unique thickening effects in acidic systems that are essentially stable (*e.g.*, do not phase separate and maintain rheological properties) even with prolonged storage.

[0002] Particularly, the invention relates to the compositions having 0.5% (% w/w) or more of at least one personal care acid or pharmaceutical acid. These compositions ideally have an acidic pH, especially a pH less than 6, and more preferably a pH less than 4, and especially preferably less than 2. These formulations find application on the skin, hair, scalp, foot, or lip of an mammal, preferably man, as a smoothing composition, a moisturizing composition, a skin firming composition, a skin lightening composition, an age-spot composition, a shampoo, or a cream for use around the eyes or mouth.

[0003] Surprisingly, the topical compositions described herein deliver the personal care and/or pharmaceutical acid with reduced skin irritation, a significant breakthrough in this field where discomfort issues are well known.

DESCRIPTION OF RELATED ART

[0004] Topical personal care and pharmaceutical compositions are products consumers around the globe have come to depend and rely on for the innumerable benefits they impart. Sold both by prescription and over-the-counter (non-prescriptive), they are applied to the exterior of the body to the skin, scalp, hair, feet, and lips. They may be cosmetic in effect, meaning they impart primarily aesthetically beneficial results (like minimizing fine lines and wrinkles), or they may relieve or cure clinical conditions (like acne vulgaris or warts), or fall somewhere between the cosmetic and medical indications. Across all these uses, many different product forms are employed, and vary

from thickened "semi-solids" like foundations, concealers, lipsticks, and lip balms, to creamy emulsions, gels, ointments, and lotions, or may be lighter "bodied" compositions such as liquid soaps, washes, and rinses. In short, topical personal care and pharmaceutical compositions are ubiquitous in today's modern world.

[0005] It has been known for some time that acidic personal and pharmaceutical compositions elicit special responses when applied topically. In this broad concept, the term *low pH* means having a pH of 6 or less. More particularly, low pH compositions can cause an increase in epidermis exfoliation to alleviate skin conditions (*e.g.*, hyperkeratosis, dry/flaky/itchy skin), enhance moisturization to help minimize the appearance of lines and wrinkles, increase dermal thickness, and increase dermal perfusion (vascular effects). A review of these actions as related to a particular type of acids, hydroxy acids and retinoids, is provided in Ramos-e-Silva, *et al.*, "Hydroxy acids and retinoids in cosmetics," *Clinics in Dermatog.*, 2001; 19:460-466, which is hereby incorporated in its entirety by reference. Also, an instructive review of alpha hydroxy acids, including the types, mechanisms of action, formulations, and treatment results, is provided by Van Scott, E.J., "Alpha-hydroxyacids in the treatment of signs of photoaging," *Clinics in Dermat.*, 1996; 14: 217-226, which also is incorporated in its entirety by reference. This article recognizes pHs in the range from 0.6 to 4.0.

[0006] While low pH topical compositions can provide useful benefits to the consumer, they can pose real challenges to the formulation scientist, production staff, and even the consumer. It is well appreciated by one skilled in the art that low pH fluids can be difficult to thicken, or to maintain a stable viscosity and/or pH. Thickeners commonly used in low pH systems include xanthan gum and magnesium aluminum silicate combinations. At addition levels to create "thick" or "stiff" consistencies, these thickeners may cause pilling (localized formulary incompatibility that leads to coagulation) or impart an unpleasant, stringy texture to the end product.

[0007] Alternatively, acrylic acid polymers, and polyacrylamides may be used. Their manufacturers usually recommend dispersing them in water and then neutralizing to attain a desired viscosity target, which simply is not possible when the product inherently remains strongly acidic.

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[0008] Other thickeners are known. For example, Carbopol® Aqua SF-1, a lightly crosslinked acrylate copolymer is sold by The Lubrizol Corporation. Product information indicates it is effective at a pH of 3.5 and higher. Also sold by The Lubrizol Corporate is Carbopol® Aqua CC Polymer, a polyacrylate-1 crosspolymer. The product white paper recommends neutralizing the polymer between a pH of 3.5 to 4.0, and, optionally, the pH can be adjusted (higher) by the addition of base. However, there still remains a need for a thickening agent that is effective at pHs of 6 or less, more preferably at very low pHs of 4 or less, and especially at extremely low pH of 2 or less.

[0009] Also known is U.S. patent 5,422,112, which discloses a thickener system including a combination of xanthan gum, magnesium aluminum silicate and polyacrylamide. The compositions are the to be particularly effective at low pH used especially for thickening alpha-hydroxy carboxylic acids and salts thereof. Typically, magnesium aluminum silicates have a recommended pH range of about 4.2 to 5.2, and typically are not the choice thickener for very low pH systems.

[0010] Similarly, U.S. patent 5,874,095 claims an enhanced skin penetration system comprising a nonionic polyacrylamide of high molecular weight, for improved topical delivery of drugs at low pH.

[0011] Further descriptions of acrylic acid thickeners are given in U.S. patents 2,883,351; 2,956,046; 3,035,004; and 3,436,378.

[0012] Poly(*N*-vinyl-2-pyrrolidone) and its salts and esters are described in U.S. patents 6,436,380; 6,197,281; 6,333,039; 6,685,952; and 7,108,860 as rheology modifiers or thickeners in personal care products.

[0013] U.S patent application 2003/0118620 teaches a thickening system for cosmetic composition of low pH, comprising a polysaccharide and taurate copolymer.

[0014] Polymeric thickeners for acidic surfactant compositions are described by U.S. patent 4,552,685, and by U.S. patent 4,529,773. However, these acidic-thickened solutions require high levels of surfactant in order to solubilize the copolymers and they have higher viscosities at pH 7 than when the pH is lowered into the acidic region.

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[0015] As shown in this summary, there remains a strong demand and need for a thickening material for low pH, very low pH, and extremely low pH systems, particularly one that maintains stable viscosity, pH, and preferably viscosity and pH. Preferably, this thickener is easy to handle, readily dispersible, and provides smooth, thickened consistencies, without being stringy or creating pilling.

[0016] Interest in thickening acidic compositions stems, in part, from the growth of acid products that consumers are demanding and using. Although the use of alpha hydroxy acids as therapy for photoaged skin was known to medical doctors by 1989 (Van Scott, E.J., "Alpha hydroxy acids: procedures for use in clinical practice, *Cutis*, 1989; 43: 222-228), a non-prescriptive market demand did not exist until 1992, when Avon launched *Anew Perfecting Complex For Face* (Avon Products, Inc. website: www.avoncompany.com/brands/skincare.html). Indeed, the U.S. Food and Drug Administration (FDA) confirms that it was not until 1992 that they received the first four registrations for new consumer products containing glycolic acid as an active ingredient (Barrows, J.N., Memorandum to the Administrative File, "Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients," Office of Cosmetics and Colors, CFSAN, FDA, September 12, 2002.) Market demand for these low pH, topically applied products grew such that by 1997 forty-two such product registrations were received by the FDA.

[0017] With the growth of this new market segment, consumers began to experience potentially harmful side effects like stinging, redness, and burning. Between 1992 and 2004 the FDA received 114 side-effect complaints (U.S. Food and Drug Administration, *Guidance: Labeling for cosmetics containing alpha hydroxy acids*, http://www.cfsan/fda/gov/guidance.html, January 10, 2005). Hence, there remains a real need for products and methods for reducing the irritation of these products while maintaining their efficacy in treating various skin and hair conditions.

[0018] As it will be explained later, the present invention is also related to lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone). This polymer was first introduced in U.S. patent 5,073,614. In that patent it is taught to be the precipitation polymerization product of *N*--vinyl-2-

pyrrolidone monomer in an organic solvent, such as an aliphatic hydrocarbon solvent (preferably cyclohexane or heptane) or an aromatic hydrocarbon (such as toluene) in the presence of about 0.2% to 1% by weight of a crosslinking agent. The fine, white powders thus produced have an aqueous gel volume of about 15 mL to 150 mL of polymer, and a Brookfield viscosity in 5% aqueous solution of at least about 10,000 cP.

[0019] This lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer also was the subject of U.S. patent 5,139,770, filed December 17, 1990 and issued August 18, 1992. In this patent examples are provided for a cream rise (pH of 4), a hair conditioner (pH of 4), and a blow dry styling lotion (pH of 6), which have been pH-adjusted by the addition of citric acid or phosphoric acid. Although not specified, one skilled in the art recognizes that the acid addition level in these formulations is small, much less than 0.5% (% w/w). As such, formulation scientists regard these acids at these levels not as *functional* acids (*e.g.*, for the *treatment* of skin or hair conditions), but, instead as *pH adjustors*, necessary to protonate the quaternary polymer(s) to make them more substantive to hair.

[0020] U.S. patent 5,716,634 teaches a lightly-crosslinked *N*-vinyl lactam polymer in form of stable, clear, flowable, homogenized hydrogel, may be used as a carrier for cosmetic/pharma active for hair or skin use. A controlled release drug-delivery composition comprising a lightly-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer is the subject of U.S. patent 5,252,611. Also, the production of lightly-crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer in an oil-in-water or water-in-oil emulsion is taught in U.S. patent 6,177,068.

[0021] A summary of some properties of light- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) is given in Shih, J.S., "Characteristics of lightly crosslinked poly(N-vinylpyrrolidone)," *Polymer Materials: Science & Engineering Preprint*, 72, 374, 1995.

[0022] Still more information on this lightly crosslinked poly(*N*-vinyl-2-pyrrolidone) polymer is given in the following U.S. patents: 5,162,417; 5,312,619; 5,622,168; 5,564,385; and 6,582,711.

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[0023] These nine U.S. patents ('770, '634, '611, '068, '417, '619, '168, '385, and '711) and the Shih article mentioned in the above paragraphs are hereby incorporated in their entirety by reference.

[0024] Hence, a first objective of the present invention is to provide a wide range of easy-to-use, topical compositions having at least one personal care or pharmaceutical acid that are effectively thickened. The invention also seeks a method to deliver the personal care/pharmaceutical acid(s), and also the use of this method to reduce the perceived irritation and sting discomfort so these compositions find greater efficacy and consumer appeal.

SUMMARY OF THE INVENTION

[0025] Surprisingly, it has been discovered that lightly- to moderately-crosslinked PVP effectively and quite elegantly thickens topical compositions having a personal care or pharmaceutical acid, even at a low pH of 6 or less, or very low pHs of 4 or less, or even extremely low pHs of 2 or less.

[0026] Additionally and even more surprising, it has been discovered that the use of these topical compositions thickened with lightly- to moderately-crosslinked PVP reduce irritation and sting discomfort compared to formulas without the lightly- to moderately-crosslinked PVP.

[0027] Hence, a first object of the present invention is to provide a thickener system particularly suited for use with acidic topical compositions, wherein the thickening agent comprises lightly- to moderately-crosslinked PVP. The topical compositions are those compositions for use on the exterior (*i.e.*, skin, hair, feet, and/or lips) of an mammal, such as man, horses, cats, and dogs. These thickened compositions serve both prescriptive and non-prescriptive markets, such as pharmaceutical and personal care compositions for skin care, hair care, foot care, scalp care, and sun care.

[0028] In these topical compositions the amount of lightly- to moderately-crosslinked PVP represents from about 0.5% to about 10% by weight of the total composition, and more preferably from about 1% to about 6% by weight. At these addition levels the low-shear ("Brookfield") viscosity typically is about 7000 cP or more, and more typically is about 10,000 cP or more.

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[0029] A second objective of the present invention is the use of these thickened, acidic compositions to deliver the personal care and/or pharmaceutical acid to the exterior of a mammal, and to use this method to reduce irritation and sting compared to compositions not having the lightly- to moderately-crosslinked PVP.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] Figure 1 is a graph of viscosity as a function of time for an acne gel produced in accordance with Example 8.

[0031] Figure 2 is a graph of pH as a function of time for an acne gel produced in accordance with Example 8.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

[0032] The present invention relates to compositions comprising at least one personal care or pharmaceutical acid, and lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) ("lightly- to moderately-crosslinked PVP") to thicken the composition. Surprisingly, it has been discovered that the lightly- to moderately-crosslinked PVP increases the viscosity of these compositions, stabilizing the viscosity and pH of these formulations that historically have proved difficult to thicken and stabilize. Lightly- to moderately-crosslinked PVP creates elegant, smooth, thickened compositions even at a pH as low as 1.3, a performance that is essentially unmatched by other thickeners.

[0033] Additionally, the invention relates to the use of these thickened compositions to deliver the acid to the skin, scalp, feet, or lips of a mammal, preferably man. Even more surprising, it has been discovered that the use of such thickened acidic compositions reduce irritation and sting discomfort compared to an equivalent formulation not having the lightly- to moderately-crosslinked PVP.

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[0034] Due to the inherent complexity in these compositions, their ingredients, product forms, and uses, it will be appreciated that definitions of terms will help describe preferred embodiments of the invention.

[0035] The term *personal care compositions* (or *formulations*) refer to compositions intended for topical use on a mammal, including, man, horses, cats, and dogs. These compositions include skin, hair, scalp, foot, or lip compositions, including those compositions that can be purchased with and without a doctor's prescription. These personal care compositions can provide any number of known benefits, such as: moisturize, prevent wrinkles, treat wrinkles, firm skin, treat blemishes, protect from ultraviolet radiation, protect from thermal damage, lighten skin color, remove dirt / soil / dead skin / blocked pores, and treat keratosis (*e.g.*, corns, calluses, and warts). The personal care compositions also may comprise other active and non-active ingredients to assist in their benefit, delivery, spreadability, emolliency, film formation, stability, and/or thickening.

[0036] The term *lightly- to moderately-crosslinked PVP*, unless otherwise noted, specifically refers to polymer essentially consisting of lightly- to moderately-crosslinked poly(*N*-vinyl-2-pyrrolidone) having at least one of the following characteristics: (1) an aqueous swelling parameter defined by its gel volume from about 15 mL/g to about 300 mL/g, more preferably from about 15 mL/g to about 250 mL/g, and most preferably from about 15 mL/g to about 150 mL/g, or (2) a Brookfield viscosity of 5% lightly- to moderately-crosslinked PVP in a liquid carrier comprising water at 25°C of at least 2,000 cP, more preferably of at least about 5,000 cP, and most preferably of at least about 10,000 cP. Disclosure for these parameter ranges is provided in U.S. patent 5,073,614 and in Shih, J.S., *et al.* (1995). Synthesis methods for the lightly- to moderately-crosslinked PVP are disclosed in a number of references, including U.S. patents 5,073,614; 5,654,385; and 6,177,068. It is appreciated by a polymer scientist skilled in the art that the method of synthesis is immaterial, inasmuch as the produced polymer achieves at least one of the abovedefined parameters.

[0037] For example, U.S. patent '614 discloses different crosslinkers and crosslinker amounts that yield lightly- to moderately-crosslinked PVP suitable for the present invention. The effect of crosslinker amount on swell volume and viscosity is graphically presented in Shih, J.S., *et al.* (1995). Thus, the lightly- to moderately-crosslinked PVP may be produced by the precipitation

polymerization method of the '614 patent, by the hydrogel method described in the '385 patent, or by the non-aqueous, heterogeneous polymerization method of the '068 patent. Certainly, other techniques are contemplated to synthesize this polymer, provided the product meets the aqueous swelling parameter and Brookfield viscosity requirements.

[0038] Final product viscosities may slightly vary for compositions containing lightly- to moderately-crosslinked PVP made by these different methods. Nonetheless, these variations are within the scope of the invention, as the lightly- to moderately-crosslinked PVPs thicken low pH compositions.

[0039] Unless otherwise specified, "lightly- to moderately-crosslinked PVP" does not refer to swellable but water-insoluble crosslinked PVP, such as the type sold into commercial trade under the trade name Polyclar® by International Specialty Products, which differs from the abovedescribed lightly- to moderately-crosslinked PVP.

[0040] The term *viscosity* refers to the proportionality coefficient between shear stress and shear rate, and describes a composition's resistance to flow. Because viscosity is dependent on shear rate, specific measurement information (such as viscometer, flow apparatus/spindle, and shear rate) is required to properly define viscosity. As used herein, *viscosity* refers to the proportionality coefficient determined from low shear rate, rotational flow, especially the viscosity measured by the Brookfield LVT and Brookfield RVT viscometers operating at 10 revolutions per minute (rpm) at 25°C. References describing the Brookfield measurement of viscosities include the following, each of which is hereby incorporated in its entirety by reference: Thibodeau, L., "Measuring viscosity of pastes," *American Laboratory News*, June 2004; McGregor, R.G., "Shelf life: does viscosity matter?" *Pharmaceutical Online*, October 31, 2007; and McGregor, R.G., "When ointments disappoint, the viscosity story," Brookfield Engineering brochure.

[0041] The term *sub-formulation* refers to a composition having two or more ingredients that is first prepared and then later blended with other ingredients as necessary. For example, sub-formulations may be made containing thickening agent(s) and liquid carrier(s) [which may or may not be solvents for the thickening agent(s)] with or without additional ingredients, and then divided into specific lots for use in specific formulation(s) at a later time.

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[0042] The term *topical* refers to any external parts of a mammal, such as man, horses, cats, and dogs, and especially man, and includes skin, hair, scalp, lips, and feet.

[0043] The term *low pH* refers to a pH of 6 or less.

[0044] The term *very low pH* refers to a pH of 4 or less.

[0045] The term *extremely low pH* refers to a pH of 2 or less.

First embodiment of the invention

[0046] In a first embodiment of the invention, topical compositions are provided that have at least one personal care acid or at least one pharmaceutical acid, and lightly- to moderately-crosslinked PVP. In these compositions the lightly- to moderately-crosslinked PVP functions, in part, as a thickener, especially to increase the low shear viscosity. It is surprising that lightly- to moderately-crosslinked PVP effectively thickens low pH, very low pH, and extremely low pH personal care and pharmaceutical compositions, with results that are essentially unmatched by existing thickeners.

[0047] By virtue of having at least one personal care or pharmaceutical acid, these topical compositions have a pH of less than 7, and more preferably, are low pH compositions. Even more preferable, these compositions have a very low pH, and in especially preferred embodiments, these compositions have an extremely low pH. Generally speaking, very low pH and extremely low pH are of greatest interest to the invention, as these compositions have proved most problematic to thicken. As it will be discussed in greater detail separately, the use of acidic topical compositions thickened with lightly- to moderately-crosslinked PVP has been discovered to produce less skin irritation and sting than identical formulations without lightly- to moderately-crosslinked PVP.

[0048] A broad selection of personal care acid and pharmaceutical acid compositions may be successfully thickened according to the invention. Generally speaking, a most preferred family is the hydroxy acid family, as their formulations most frequently exhibit acidic pHs that are difficult to thicken and stabilize. Hydroxy acids can be divided into four subfamilies: alpha hydroxy acids,

beta hydroxy acids, alpha and beta hydroxy acids, and polyhydroxy acids.

[0049] Alpha hydroxy acids are frequently employed in skin lotions and the like, as they are among the most useful exfoliation agents. By definition, alpha hydroxy acids possess a carboxylic acid group with a hydroxyl group on the adjacent carbon atom. Both naturally occurring and synthetic alpha hydroxy acids are known and suitable for use in the invention. Examples of alpha hydroxy acids include, without limitation: alpha hydroxyethanoic acid, alpha hydroxyoctanoic acid, alpha hydroxycaprylic acid, ascorbic acid, adipic acid, caprylic acid, capric acid, glycolic acid, lactic acid, lauric acid, mandelic acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, ricinoleic acid, oleic acid, tartaric acid, elaidic acid, and erucic acid.

[0050] Most preferred are alpha hydroxy acids that exhibit high epidermis penetration so that they may exert a maximum effect on the underlying dermis layer. Thus, the most effective alpha hydroxy acids are those of small molecular weight, such as glycolic acid and lactic acid. This preference, however, is not to say that the invention does not work in thickening higher molecular weight acids. Rather, this preference merely recognizes a special class of hydroxy acids that are used in many personal care and pharmaceutical compositions.

[0051] Like their alpha counterparts, beta hydroxy acids also find utility in the invention and in skin care products due to their ability to penetrate the epidermis and activity in the dermal layer. Beta hydroxy acids are those molecules having a carboxylic acid group and a hydroxyl group separated by two carbon atoms. Again, both naturally occurring and synthetic beta hydroxy acids are known and may be used in the invention's compositions. Specific examples of beta hydroxy acids include, but are not limited to: beta hydroxybutanoic acid, tropic acid, trethocanic acid, salicylic acid, and 5-(*n*-octanoyl) salicylic acid.

[0052] Also for use in the thickened topical compositions are alpha beta hydroxy acids. As the same suggests, these acids contain at least one alpha hydroxy acid group and one beta hydroxy acid group. Examples of alpha beta hydroxy acids include: malic acid, citric acid, and tartaric acid.

[0053] A final member of the hydroxy acid family is the polyhydroxy acid, which, as the name suggests, are molecules having at least one carboxylic acid functional group and more than 1

hydroxyl group. Polyhydroxy acids also may be naturally occurring or synthetically manufacturered, and have a higher molecular weight than glycolic acid or lactic acid. As a result, polyhydroxy acids are less penetrating than these two alpha hydroxy acids, and, as a result, provide gentler skin effects, typically with reduced irritation. Examples of suitable polyhydroxy acids include lactobionic acid, galactose, and gluconic acid.

[0054] Other personal care acids and pharmaceutical acids are known and are contemplated for use in the thickened compositions of the invention. Non-hydroxy acids that may be used are: aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N*'-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, etidronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

[0055] In order to achieve desired product performance, mixtures of different acids also may be thickened, as well as combinations of acids and the corresponding salts. Suitable such salts include the alkali metal salts of phosphoric and sulphuric acids, *e.g.* potassium biphosphate and sodium bisulphate.

[0056] The thickened topical compositions of the invention may be used where ever acidic personal care and acidic pharmaceutical preparations find utility. Accordingly, the amount of lightly- to moderately-crosslinked PVP in the composition depends on a variety of parameters, including the amount and type of acid(s), other ingredients, and the desired product form, delivery, and consumer "thickness" acceptance. For example, the thickened compositions may be an anti-aging cream, a lotion for skin blemishes, a smoothing lotion, a moisturizing composition, a skin lightening treatment, a shampoo, or a cream for use around the eyes or mouth. In these formulations the amount of lightly- to moderately-crosslinked PVP may vary from about 0.1% to about 10% (w/w) of the total formulation. More typically, however, the amount of lightly- to moderately-crosslinked PVP varies from about 1% to about 6% (w/w) of the total formulation. As illustrated in Examples 2–6, thickened acid systems containing from 43% to 71% glycolic acid were effectively thickened to viscosities ranging from 15,000 cP to 37,000 cP with the addition of 4.5% lightly- to moderately-crosslinked PVP.

[0057] At these addition levels of lightly- to moderately-crosslinked PVP, the thickened low pH

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compositions typically have a Brookfield viscosity, as measured at 10 rpm and 25°C using an appropriate spindle (*e.g.*, T-C or T-E), from about 1,000 cP to about 100,000 cP. (Of course, the product Brookfield viscosity depends on the panoply of factors outlined in the preceding paragraph.) More preferably, based on the contemplated product forms, the compositions have a Brookfield viscosity from about 10,000 cP to 50,000 cP.

[0058] Because of the stabilized viscosity and pH provided by lightly- to moderately-crosslinked PVP in these low pH formulations, compositions comprising this thickener may be a sub-formulation or a complete formulation. Considering the challenges facing production scheduling, batch preparation, and formulation changes, for example, it may be advantageous to prepare a sub-formulation batch having the lightly- to moderately-crosslinked PVP, and then use portions of it at some later time to prepare one or more final formulations. Alternatively, a complete formulation with the lightly- to moderately-crosslinked PVP may be made at essentially in one batch. The compositions of Examples 2–6 may be viewed as examples of sub-formulations if they are not desired as stand-along gel preparations (*e.g.*, for skin care).

[0059] It was mentioned earlier that the amount of lightly- to moderately-crosslinked PVP in the thickened, acidic formulation depends on a number of factors, including the desired product form. The compositions do not produce "pilling" (incompatibilities and/or phase separations/agglomeration resulting in lumps) nor impart a stringy texture to the composition even at extremely low pH. This relationship between lightly- to moderately-crosslinked PVP and viscosity cannot be overstated, as thickeners generally are not known for such low pH systems.

[0060] The thickening additive compositions in accordance with this disclosure can be easily prepared by conventional methods known to persons of ordinary skill in the art, employing methods such as, simple mixing, blending, and homogenization using physical means or heat blending.

Second embodiment of the invention

[0061] In a second embodiment of the invention, the thickened topical compositions are used to deliver the personal care and/or pharmaceutical acid(s) to the skin, hair, scalp, foot, or lip of a mammal in need of treatment. As discussed for the first embodiment of the invention, it is preferred

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for this second embodiment that at least one personal care acid or at least one pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-N'-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

[0062] Again, especially preferred uses include those compositions having hydroxy acids, such as alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

[0063] As an extension of this use, it has been discovered that the use of these thickened topical compositions reduce the discomfort of irritation and sting compared to an equivalent formulation without lightly- to moderately-crosslinked PVP. The merit of this claim was provided from three independent, third-party clinical laboratory evaluations, as discussed in Examples 10–12. Without being bound to theory, one school of thought is that lightly- to moderately-crosslinked PVP in these formulas creates a gel network with the acid(s), moderates its release, and thus makes these compositions gentler on skin.

[0064] Because irritation/sting was evaluated using the simple formulas of Examples 10–12, it will be appreciated by one skilled in the art that significant formulation development may be pursued to maximize the composition and use benefits embraced by this invention. For example, products may be formulated with exfoliation, firming, moisturizing, and/or dermal perfusion effect(s) comparable to existing products (without lightly- to moderately-crosslinked PVP), but which reduce or eliminate irritation and/or sting. Such products may be found to be exceedingly gentle even on the most sensitive of skin.

[0065] Alternatively, products can be formulated that maintain the level of irritation and/or sting of current products (without lightly- to moderately-crosslinked PVP), but which provide greater exfoliation, firming, moisturizing, and/or dermal perfusion effect(s). These products may be aimed at enhanced-performance product lines, or compositions intended to be used under the care of a physician.

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Optional: Additional formulation ingredients and adjuvants

[0066] Due to the requirements of end performance, it is expected that the topical compositions of this invention will be used together with other additives to further enhance the properties of the finished product. Such ingredients may be incorporated without altering the scope of the current invention, and may be included in order to produce the necessary products.

[0067] These topical formulations inevitably have a liquid or liquid-like carrier that aides to distribute, disperse, and/or dissolve the formulation ingredients, including the lightly- to moderately-crosslinked PVP. Selection of these carriers is not limited, inasmuch as the formulations have at least one personal care acid or at least one pharmaceutical acid, and examples of liquid carriers include water, alcohols, oils, esters, and blends thereof.

[0068] The composition of the invention also can contain one or more additional additives chosen from conditioning agents, protecting agents, such as, for example, hydrosoluble, antiradical agents, antioxidants, vitamins, ultraviolet absorbers, and pro-vitamins, fixing agents, oxidizing agents, reducing agents, dyes, cleansing agents, anionic, cationic, nonionic and amphoteric surfactants, thickeners, perfumes, pearlizing agents, stabilizers, pH adjusters, filters, preservatives, cationic and nonionic polyether associative polyurethanes, polymers other than the cationic polymer described herein, vegetable oils, mineral oils, synthetic oils, polyols such as glycols and glycerol, silicones, aliphatic alcohols, colorants, bleaching agents, highlighting agents and sequestrants. These additives are present in the composition according to the invention in proportions that may range from 0% to 20% by weight in relation to the total weight of the composition. The precise amount of each additive may be easily determined by an expert in the field according to its nature and its function.

[0069] When the final product aims to protect the user from ultraviolet radiation, it may be desirable to include one or more UV absorbers. In this context, the terms *ultraviolet* and *UV* mean electromagnetic radiation, especially solar electromagnetic radiation, with a wavelength from about 100 nm to about 400 nm, and includes the UV-A, UV-B, and UV-C subclassifications of such radiation. The term *UV-A* means ultraviolet electromagnetic radiation with a wavelength from

about 320 nm to about 400 nm, and includes UV-A1 (from about 340 nm to about 400 nm) and UV-A2 (from about 320 nm to about 340 nm).

The term *UV-B* means ultraviolet electromagnetic radiation with a wavelength from about 290 nm to about 320 nm. The term *UV-C* means ultraviolet electromagnetic radiation with a wavelength from about 200 nm to about 290 nm. Finally, the term *UV absorber* means any entity that absorbs, scatters, and/or reflects any wavelength of UV radiation.

[0070] Suitable UV absorbers that may be included in the topical compositions and uses of the invention most likely will depend on local regulations. Because the rules governing the names and usage levels evolve over time, it is impossible to include every UV absorber that may be used with the invention. Typical UV absorbers include, without limitation: octyl salicylate; pentyl dimethyl PABA; octyl dimethyl PABA; benzophenone-1; benzophenone-6; 2-(2H-benzotriazole-2-yl)-4,6-di-*tert*-pentylphenol; ethyl-2-cyano-3,3-diphenylacrylate; homomenthyl salicylate; bis-ethylhexyloxyphenol methoxyphenyl triazine; methyl-(1,2,2,6,6-pentamethyl-4-piperidyl)-sebacate; 2-(2H-benzotriazole-2-yl)-4-methylphenol; diethylhexyl butamido triazone; amyl dimethyl PABA; 4,6-bis(octylthiomethyl)-*o*-cresol; CAS number 65447-77-0; red petroleum; ethylhexyl triazone; octocrylene; isoamyl-*p*-methoxycinnamate; drometrizole; titanium dioxide; 2,4-di-*tert*-butyl-6-(5-chloro-2H-benzotriazole-2-yl)-phenol; 2-hydroxy-4-octyloxybenzophenone; benzophenone-2; diisopropyl methylcinnamate; PEG-25 PABA; 2-(1,1-dimethylethyl)-6-[[3-(1,1-demethylethyl)-2-hydroxy-5-methylphenyl]methyl-4-methylphenyl acrylate; drometrizole trisiloxane; menthyl anthranilate; butyl methoxydibenzoylmethane; 2-ethoxyethyl *p*-methoxycinnamate; benzylidene camphor sulfonic acid; dimethoxyphenyl-[1-(3,4)]-4,4-dimethyl 1,3-pentanedione; zinc oxide; *N,N'*-hexane-1,6-diylbis[3-(3,5-di-*tert*-butyl-4-hydroxyphenylpropionamide)]; pentaerythritol tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]; 2,6-di-*tert*-butyl-4-[4,6-bis(octylthio)-1,3,5-triazin-2-ylamino] phenol; 2-(2H-benzotriazole-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol; trolamine salicylate; diethylanolamine *p*-methoxycinnamate; polysilicone-15; CAS number 152261-33-1; 4-methylbenzylidene camphor; bisoctrizole; *N*-phenyl-benzenamine; reaction products with 2,4,4-trimethylpentene; sulisobenzone; (2-ethylhexyl)-2-cyano-3,3-diphenylacrylate; digalloyl trioleate; polyacrylamido methylbenzylidene camphor; glyceryl ethylhexanoate dimethoxycinnamate; 1,3-bis-[(2'-cyano-3',3'-diphenylacryloyl)oxy]-2,2-bis-{[(2'-cyano-bis-(2,2,6,6-tetramethyl-4-piperidyl)-sebacate; benzophenone-5; 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; hexamethylendiamine; benzophenone-8; ethyl-4-bis(hydroxypropyl)

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aminobenzoate; 6-*tert*-butyl-2-(5-chloro-2H-benzotriazole-2-yl)-4-methylphenol; *p*-aminobenzoic acid; 3,3',3'',5,5',5''-hexa-*tert*-butyl-α-α'-α''-(mesitylene-2,4,6-triyl)tri-*p*-cresol; lawsone with dihydroxyacetone; benzophenone-9; benzophenone-4; ethylhexyl dimethoxy benzylidene dioxoimidazoline propionate; *N,N'*-bisformyl-N,N'-bis-(2,2,6,6-tetramethyl-4-piperidinyl)-; 3-benzylidene camphor; terephthalylidene dicamphor sulfonic acid; camphor benzalkonium methosulfate; bisdisulizole disodium; etocrylene; ferulic acid; 2-(2H-benzotriazole-2-yl)-4-(1,1,3,3-tetramethylbutyl)-phenol; 4,6-bis(dodecylthiomethyl)-*o*-cresol; β-2-glucopyranoxy propyl hydroxy benzophenone; phenylbenzimidazole sulfonic acid; benzophenone-3; diethylamine hydroxybenzoyl hexylbenzoate; 3',3'-diphenylacryloyl)oxy]methyl}-propane; ethylhexyl *p*-methoxycinnamate, and blends thereof.

[0071] For example, the compositions according to the invention may be used to moisturize, soothe, retain moisture, and/or smooth skin, especially skin of the hands, elbows, and feet, and around the eyes and mouth. Highly preferred are thickened formulations that are non-greasy, such as lotions having glycerin, caprylic/capric triglycerides, hydrogenated cocoglycerides, and/or one or more vegetable oils (*e.g.*, helianthus oil, soybean oil, linseed oil, and olive oil).

[0072] Any known conditioning agent is useful in the personal care compositions of this invention. Conditioning agents function to improve the cosmetic properties of the hair, particularly softness, thickening, untangling, feel, and static electricity and may be in liquid, semi-solid, or solid form such as oils, waxes, or gums. Similarly, any known skin altering agent is useful in the compositions of this invention. Preferred conditioning agents include cationic polymers, cationic surfactants and cationic silicones.

[0073] Conditioning agents may be chosen from synthesis oils, mineral oils, vegetable oils, fluorinated or perfluorinated oils, natural or synthetic waxes, silicones, cationic polymers, proteins and hydrolyzed proteins, ceramide type compounds, cationic surfactants, fatty amines, fatty acids and their derivatives, as well as mixtures of these different compounds.

[0074] The synthesis oils include polyolefins, *e.g.*, poly-α-olefins such as polybutenes, polyisobutenes and polydecenes. The polyolefins can be hydrogenated.

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[0075] The mineral oils suitable for use in the compositions of the invention include hexadecane and oil of paraffin.

[0076] A list of suitable animal and vegetable oils comprises sunflower, corn, soy, avocado, jojoba, squash, raisin seed, sesame seed, walnut oils, fish oils, glycerol tricaprocaprylate, Purcellin oil or liquid jojoba, and blends thereof.

[0077] Suitable natural or synthetic oils include eucalyptus, lavender, vetiver, litsea cubeba, lemon, sandalwood, rosemary, chamomile, savory, nutmeg, cinnamon, hyssop, caraway, orange, geranium, cade, and bergamot.

[0078] Suitable natural and synthetic waxes include carnauba wax, candelilla wax, alfa wax, paraffin wax, ozokerite wax, vegetable waxes such as olive wax, rice wax, hydrogenated jojoba wax, absolute flower waxes such as black currant flower wax, animal waxes such as bees wax, modified bees wax (cerabellina), marine waxes and polyolefin waxes such as polyethylene wax, and blends thereof.

[0079] The cationic polymers that may be used as a conditioning agent according to the invention are those known to improve the cosmetic properties of hair treated by detergent compositions. The expression "cationic polymer" as used herein, indicates any polymer containing cationic groups and/or ionizable groups in cationic groups. The cationic polymers used generally have a molecular weight the average number of which falls between about 500 Da and 5,000,000 Da and preferably between 1000 Da and 3,000,000 Da.

[0080] The preferred cationic polymers are chosen from among those containing units including primary, secondary, tertiary, and/or quaternary amine groups that may either form part of the main polymer chain or a side chain.

[0081] Useful cationic polymers include known polyamine, polyaminoamide, and quaternary polyammonium types of polymers, such as:

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[0082] (1) homopolymers and copolymers derived from acrylic or methacrylic esters or amides. The copolymers can contain one or more units derived from acrylamides, methacrylamides, diacetone acrylamides, acrylamides and methacrylamides, acrylic or methacrylic acids or their esters, vinyllactams such as vinyl pyrrolidone or vinyl caprolactam, and vinyl esters. Specific examples include: copolymers of acrylamide and dimethyl amino ethyl methacrylate quaternized with dimethyl sulfate or with an alkyl halide; copolymers of acrylamide and methacryloyl oxyethyl trimethyl ammonium chloride; the copolymer of acrylamide and methacryloyl oxyethyl trimethyl ammonium methosulfate; copolymers of vinyl pyrrolidone/dialkylaminoalkyl acrylate or methacrylate, optionally quaternized, such as the products sold under the name Gafquat® by International Specialty Products; the dimethyl amino ethyl methacrylate/vinyl caprolactam/vinyl pyrrolidone terpolymers, such as the product sold under the name Gaffix® VC 713 by International Specialty Products; the vinyl pyrrolidone/methacrylamidopropyl dimethylamine copolymer, marketed under the name Styleze® CC 10 by International Specialty Products; and the vinyl pyrrolidone/quaternized dimethyl amino propyl methacrylamide copolymers such as the product sold under the name Gafquat® HS 100 by International Specialty Products (Wayne, NJ).

[0083] (2) derivatives of cellulose ethers containing quaternary ammonium groups, such as hydroxy ethyl cellulose quaternary ammonium that has reacted with an epoxide substituted by a trimethyl ammonium group.

[0084] (3) derivatives of cationic cellulose such as cellulose copolymers or derivatives of cellulose grafted with a hydrosoluble quaternary ammonium monomer, as described in U.S. patent 4,131,576, such as the hydroxy alkyl cellulose, and the hydroxymethyl-, hydroxyethyl- or hydroxypropyl- cellulose grafted with a salt of methacryloyl ethyl trimethyl ammonium, methacrylamidopropyl trimethyl ammonium, or dimethyl diallyl ammonium.

[0085] (4) cationic polysaccharides such as described in U.S. patents 3,589,578 and 4,031,307, guar gums containing cationic trialkyl ammonium groups and guar gums modified by a salt, *e.g.*, chloride of 2,3-epoxy propyl trimethyl ammonium.

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[0086] (5) polymers composed of piperazinyl units and alkylene or hydroxy alkylene divalent radicals with straight or branched chains, possibly interrupted by atoms of oxygen, sulfur, nitrogen, or by aromatic or heterocyclic cycles, as well as the products of the oxidation and/or quaternization of such polymers.

[0087] (6) water-soluble polyamino amides prepared by polycondensation of an acid compound with a polyamine. These polyamino amides may be reticulated.

[0088] (7) derivatives of polyamino amides resulting from the condensation of polyalcoylene polyamines with polycarboxylic acids followed by alcoylation by bi-functional agents.

[0089] (8) polymers obtained by reaction of a polyalkylene polyamine containing two primary amine groups and at least one secondary amine group with a dioxycarboxylic acid chosen from among diglycolic acid and saturated dicarboxylic aliphatic acids having 3 to 8 atoms of carbon. Such polymers are described in U.S. Patents 3,227,615 and 2,961,347.

[0090] (9) the cyclopolymers of alkyl dialyl amine or dialkyl diallyl ammonium such as the homopolymer of dimethyl diallyl ammonium chloride and copolymers of diallyl dimethyl ammonium chloride and acrylamide.

[0091] (10) quaternary diammonium polymers such as hexadimethrine chloride.

[0092] (11) quaternary polyammoonium polymers, including, for example, Mirapol® A 15, Mirapol® AD1, Mirapol® AZ1, and Mirapol® 175 products sold by Miranol .

[0093] (12) the quaternary polymers of vinyl pyrrolidone and vinyl imidazole such as the products sold under the names Luviquat® FC 905, FC 550, and FC 370 by BASF Corporation.

[0094] (13) quaternary polyamines.

[0095] (14) reticulated polymers known in the art.

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[0096] Other cationic polymers that may be used within the context of the invention are cationic proteins or hydrolyzed cationic proteins, polyalkyleneimines such as polyethyleneimines, polymers containing vinyl pyridine or vinyl pyridinium units, condensates of polyamines and epichlorhydrins, quaternary polyurethanes, and derivatives of chitin.

[0097] Preferred cationic polymers are derivatives of quaternary cellulose ethers, the homopolymers and copolymers of dimethyl diallyl ammonium chloride, quaternary polymers of vinyl pyrrolidone and vinyl imidazole, and mixtures thereof.

[0098] The conditioning agent can be any silicone known by those skilled in the art to be useful as a conditioning agent. The silicones suitable for use according to the invention include polyorganosiloxanes that are insoluble in the composition. The silicones may be present in the form of oils, waxes, resins, or gums. They may be volatile or non-volatile. The silicones can be selected from polyalkyl siloxanes, polyaryl siloxanes, polyalkyl aryl siloxanes, silicone gums and resins, and polyorgano siloxanes modified by organofunctional groups, and mixtures thereof.

[0099] Suitable polyalkyl siloxanes include polydimethyl siloxanes with terminal trimethyl silyl groups or terminal dimethyl silanol groups (dimethiconol) and polyalkyl (C_1-C_{20}) siloxanes.

[00100] Suitable polyalkyl aryl siloxanes include polydimethyl methyl phenyl siloxanes and polydimethyl diphenyl siloxanes, linear or branched.

[00101] The silicone gums suitable for use herein include polydiorganosiloxanes preferably having a number-average molecular weight between 200,000 Da and 1,000,000, Da used alone or mixed with a solvent. Examples include polymethyl siloxane, polydimethyl siloxane/methyl vinyl siloxane gums, polydimethyl siloxane/diphenyl siloxane, polydimethyl siloxane/phenyl methyl siloxane and polydimethyl siloxane/diphenyl siloxane/methyl vinyl siloxane.

[00102] Suitable silicone resins include silicones with a dimethyl/trimethyl siloxane structure and resins of the trimethyl siloxysilicate type.

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[00103] The organo-modified silicones suitable for use in the invention include silicones such as those previously defined and containing one or more organofunctional groups attached by means of a hydrocarbon radical and grafted siliconated polymers. Particularly preferred are amino functional silicones.

[00104] The silicones may be used in the form of emulsions, nano-emulsions, or micro-emulsions.

[00105] The conditioning agent can be a protein or hydrolyzed cationic or non-cationic protein. Examples of these compounds include hydrolyzed collagens having triethyl ammonium groups, hydrolyzed collagens having trimethyl ammonium and trimethyl stearyl ammonium chloride groups, hydrolyzed animal proteins having trimethyl benzyl ammonium groups (benzyltrimonium hydrolyzed animal protein), hydrolyzed proteins having groups of quaternary ammonium on the polypeptide chain, including at least one C_1-C_{18} alkyl.

[00106] Hydrolyzed proteins include Croquat L, in which the quaternary ammonium groups include a C_{12} alkyl group, Croquat M, in which the quaternary ammonium groups include C_{10}-C_{18} alkyl groups, Croquat S in which the quaternary ammonium groups include a C_{18} alkyl group and Crotein Q in which the quaternary ammonium groups include at least one C_1-C_{18} alkyl group. These products are sold by Croda.

[00107] The conditioning agent can comprise quaternized vegetable proteins such as wheat, corn, or soy proteins such as cocodimonium hydrolyzed wheat protein, laurdimonium hydrolyzed wheat protein and steardimonium hydrolyzed wheat protein, 2-*N*-stearoyl amino-octadecane-1,3-diol, 2-*N*-behenoyl amino-octadecane-1,3-diol, 2-*N*-[2-hydroxy-palmitoyl]-amino-octadecane-1,3-diol, 2-*N*-stearoyl amino-octadecane-1,3,4-triol, *N*-stearoyl phytosphingosine, 2-*N*-palmitoyl amino-hexadecane-1,3-diol, bis-(*N*-hydroxy ethyl N-cetyl) malonamide, *N*-(2-hydroxy ethyl)-*N*-(3-cetoxyl-2-hydroxy propyl) amide of cetylic acid, *N*-docosanoyl *N*-methyl-D-glucamine and mixtures of such compounds.

[00108] The conditioning agent can be a cationic surfactant such as a salt of a primary, secondary, or tertiary fatty amine, optionally polyoxyalkylenated, a quaternary ammonium salt, a derivative of

imadazoline, or an amine oxide. Suitable examples include mono-, di-, or tri- alkyl quaternary ammonium compounds with a counterion such as a chloride, methosulfate, tosylate, etc. including, but not limited to, cetrimonium chlocide, dicetyldimonium chloride, behentrimonium methosulfate, and the like. The presence of a quaternary ammonium compound in conjunction with the polymer described above reduces static and enhances combing of hair in the dry state. The polymer also enhances the deposition of the quaternary ammonium compound onto the hair substrate thus enhancing the conditioning effect of hair.

[00109] The conditioning agent can be any fatty amine known to be useful as a conditioning agent; *e.g.* dodecyl, cetyl or stearyl amines, such as stearamidopropyl dimethylamine.

[00110] The conditioning agent can be a fatty acid or derivatives thereof known to be useful as conditioning agents. Suitable fatty acids include myristic acid, palmitic acid, stearic acid, behenic acid, oleic acid, linoleic acid, and isostearic acid. The derivatives of fatty acids include carboxylic ester acids including mono-, di-, tri- and tetra- carboxylic acids.

[00111] The conditioning agent can be a fluorinated or perfluorinated oil. The fluoridated oils may also be fluorocarbons such as fluoramines, *e.g.*, perfluorotributylamine, fluoridated hydrocarbons, such as perfluorodecahydronaphthalene, fluoroesters, and fluoroethers.

[00112] Of course, mixtures of two or more conditioning agents can be used.

[00113] The conditioning agent or agents can be present in an amount of 0.001% to 20%, preferably from 0.01% to 10%, and even more preferably from 0.1% to 3% by weight based on the total weight of the final composition.

[00114] The antioxidants or antiradical agents can be selected from phenols such as BHA (*tert*-butyl-4-hydroxy anisole), BHT (2,6-di-*tert*-butyl-p-cresol), TBHQ (*tert*-butyl hydroquinone), polyphenols such as proanthocyanodic oligomers, flavonoids, hindered amines such as tetra amino piperidine, erythorbic acid, polyamines such as spermine, cysteine, glutathione, superoxide dismutase, and lactoferrin.

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[00115] The vitamins can be selected from ascorbic acid (vitamin C), vitamin E, vitamin E acetate, vitamin E phosphate, B vitamins such as B3 and B5, niacin, vitamin A, and derivatives thereof. The provitamins can be selected from panthenol and retinol.

[00116] The protecting agent can be present in an amount 0.001% to 20% by weight, preferably from 0.01% to 10% by weight, and more preferably 0.1 to 5% by weight of the total weight of the final composition.

[00117] In addition, the compositions according to the invention advantageously include at least one surfactant, which can be present in an amount of 0.1% and 60% preferably 1% and 40%, and more preferably 5% and 30% by weight based on the total weight of the composition. The surfactant may be chosen from among anionic, amphoteric, or non-ionic surfactants, or mixtures of them known to be useful in personal care compositions.

[00118] Additional thickeners or viscosity increasing agents may be included in the composition of the invention, such as: Acetamide MEA; acrylamide/ethalkonium chloride acrylate copolymer; acrylamide/ethyltrimonium chloride acrylate/ethalkonium chloride acrylate copolymer; acrylamides copolymer; acrylamide/sodium acrylate copolymer; acrylamide/sodium acryloyldimethyltaurate copolymer; acrylates/acetoacetoxyethyl methacrylate copolymer; acrylates/beheneth-25 methacrylate copolymer; acrylates/C_{10}-C_{30} alkyl acrylate crosspolymer; acrylates/ceteth-20 itaconate copolymer; acrylates/ceteth-20 methacrylate copolymer; acrylates/laureth-25 methacrylate copolymer; acrylates/palmeth-25 acrylate copolymer; acrylates/palmeth-25 itaconate copolymer; acrylates/steareth-50 acrylate copolymer; acrylates/steareth-20 itaconate copolymer; acrylates/steareth-20 methacrylate copolymer; acrylates/stearyl methacrylate copolymer; acrylates/vinyl isodecanoate crosspolymer; acrylic acid/acrylonitrogens copolymer; adipic acid/methyl DEA crosspolymer; agar; agarose; alcaligenes polysaccharides; algin; alginic acid; almondamide DEA; almondamidopropyl betaine; aluminum/magnesium hydroxide stearate; ammonium acrylates/acrylonitrogens copolymer; ammonium acrylates copolymer; ammonium acryloyldimethyltaurate/vinyl formamide copolymer; ammonium acryloyldimethyltaurate/VP copolymer; ammonium alginate; ammonium chloride; ammonium polyacryloyldimethyl taurate; ammonium sulfate; amylopectin; apricotamide DEA; apricotamidopropyl betaine; arachidyl

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alcohol; arachidyl glycol; arachis hypogaea (peanut) flour; ascorbyl methylsilanol pectinate; astragalus gummifer gum; attapulgite; avena sativa (oat) kernel flour; avocadamide DEA; avocadamidopropyl betaine; azelamide MEA; babassuamide DEA; babassuamide MEA; babassuamidopropyl betaine; behenamide DEA; behenamide MEA; behenamidopropyl betaine; behenyl betaine; bentonite; butoxy chitosan; caesalpinia spinosa gum; calcium alginate; calcium carboxymethyl cellulose; calcium carrageenan; calcium chloride; calcium potassium carbomer; calcium starch octenylsuccinate; C20-40 alkyl stearate; canolamidopropyl betaine; capramide DEA; capryl/capramidopropyl betaine; carbomer; carboxybutyl chitosan; carboxymethyl cellulose acetate butyrate; carboxymethyl chitin; carboxymethyl chitosan; carboxymethyl dextran; carboxymethyl hydroxyethylcellulose; carboxymethyl hydroxypropyl guar; carnitine; cellulose acetate propionate carboxylate; cellulose gum; ceratonia siliqua gum; cetearyl alcohol; cetyl alcohol; cetyl babassuate; cetyl betaine; cetyl glycol; cetyl hydroxyethylcellulose; chimyl alcohol; cholesterol/HDI/pullulan copolymer; cholesteryl hexyl dicarbamate pullulan; citrus aurantium dulcis (orange) peel extract; cocamide DEA; cocamide MEA; cocamide MIPA; cocamidoethyl betaine; cocamidopropyl betaine; cocamidopropyl hydroxysultaine; coco-betaine; coco-hydroxysultaine; coconut alcohol; coco/oleamidopropyl betaine; coco-Sultaine; cocoyl sarcosinamide DEA; cornamide/cocamide DEA; cornamide DEA; croscarmellose; crosslinked bacillus/glucose/sodium glutamate ferment; cyamopsis tetragonoloba (guar) gum; decyl alcohol; decyl betaine; dehydroxanthan gum; dextrin; dibenzylidene sorbitol; diethanolaminooleamide DEA; diglycol/CHDM/isophthalates/SIP copolymer; dihydroabietyl behenate; dihydrogenated tallow benzylmonium hectorite; dihydroxyaluminum aminoacetate; dimethicone/PEG-10 crosspolymer; dimethicone/PEG-15 crosspolymer; dimethicone propyl PG-betaine; dimethylacrylamide/acrylic acid/polystyrene ethyl methacrylate copolymer; dimethylacrylamide/sodium acryloyldimethyltaurate crosspolymer; disteareth-100 IPDI; DMAPA acrylates/acrylic acid/acrylonitrogens copolymer; erucamidopropyl hydroxysultaine; ethylene/sodium acrylate copolymer; gelatin; gellan gum; glyceryl alginate; glycine soja (soybean) flour; guar hydroxypropyltrimonium chloride; hectorite; hyaluronic acid; hydrated silica; hydrogenated potato starch; hydrogenated tallow; hydrogenated tallowamide DEA; hydrogenated tallow betaine; hydroxybutyl methylcellulose; hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer; hydroxyethylcellulose; hydroxyethyl chitosan; hydroxyethyl ethylcellulose; hydroxyethyl stearamide-MIPA; hydroxylauryl/hydroxymyristyl betaine; hydroxypropylcellulose; hydroxypropyl chitosan; hydroxypropyl ethylenediamine carbomer; hydroxypropyl guar; hydroxypropyl methylcellulose; hydroxypropyl methylcellulose stearoxy

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ether; hydroxypropyl starch; hydroxypropyl starch phosphate; hydroxypropyl xanthan gum; hydroxystearamide MEA; isobutylene/sodium maleate copolymer; isostearamide DEA; isostearamide MEA; isostearamide mIPA; isostearamidopropyl betaine; lactamide MEA; lanolinamide DEA; lauramide DEA; lauramide MEA; lauramide MIPA; lauramide/myristamide DEA; lauramidopropyl betaine; lauramidopropyl hydroxysultaine; laurimino bispropanediol; lauryl alcohol; lauryl betaine; lauryl hydroxysultaine; lauryl/myristyl glycol hydroxypropyl ether; lauryl sultaine; lecithinamide DEA; linoleamide DEA; linoleamide MEA; linoleamide MIPA; lithium magnesium silicate; lithium magnesium sodium silicate; macrocystis pyrifera (kelp); magnesium alginate; magnesium/aluminum/hydroxide/carbonate; magnesium aluminum silicate; magnesium silicate; magnesium trisilicate; methoxy PEG-22/dodecyl glycol copolymer; methylcellulose; methyl ethylcellulose; methyl hydroxyethylcellulose; microcrystalline cellulose; milkamidopropyl betaine; minkamide DEA; minkamidopropyl betaine; MIPA-myristate; montmorillonite; Moroccan lava clay; myristamide DEA; myristamide MEA; myristamide MIPA; myristamidopropyl betaine; myristamidopropyl hydroxysultaine; myristyl alcohol; myristyl betaine; natto gum; nonoxynyl hydroxyethylcellulose; oatamide MEA; oatamidopropyl betaine; octacosanyl glycol isostearate; octadecene/MA copolymer; oleamide DEA; oleamide MEA; oleamide MIPA; oleamidopropyl betaine; oleamidopropyl hydroxysultaine; oleyl betaine; olivamide DEA; olivamidopropyl betaine; oliveamide MEA; palmamide DEA; palmamide MEA; palmamide MIPA; palmamidopropyl betaine; palmitamide DEA; palmitamide MEA; palmitamidopropyl betaine; palm kernel alcohol; palm kernelamide DEA; palm kernelamide MEA; palm kernelamide MIPA; palm kernelamidopropyl betaine; peanutamide MEA; peanutamide MIPA; pectin; PEG-800; PEG-crosspolymer; PEG-150/decyl alcohol/SMDI copolymer; PEG-175 diisostearate; PEG-190 distearate; PEG-15 glyceryl tristearate; PEG-140 glyceryl tristearate; PEG-240/HDI copolymer bis-decyltetradeceth-20 ether; PEG-100/IPDI copolymer; PEG-180/laureth-50/TMMG copolymer; PEG-10/lauryl dimethicone crosspolymer; PEG-15/lauryl dimethicone crosspolymer; PEG-2M; PEG-5M; PEG-7M; PEG-9M; PEG-14M; PEG-20M; PEG-23M; PEG-25M; PEG-45M; PEG-65M; PEG-90M; PEG-115M; PEG-160M; PEG-180M; PEG-120 methyl glucose trioleate; PEG-180/octoxynol-40/TMMG copolymer; PEG-150 pentaerythrityl tetrastearate; PEG-4 rapeseedamide; PEG-150/stearyl alcohol/SMDI copolymer; phaseolus angularis seed powder; polianthes tuberosa extract; polyacrylate-3; polyacrylic acid; polycyclopentadiene; polyether-1; polyethylene/isopropyl maleate/MA copolyol; polyglyceryl-3 disiloxane dimethicone; polyglyceryl-3 polydimethylsiloxyethyl dimethicone; polymethacrylic acid; polyquaternium-52; polyvinyl

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alcohol; potassium alginate; potassium aluminum polyacrylate; potassium carbomer; potassium carrageenan; potassium chloride; potassium palmate; potassium polyacrylate; potassium sulfate; potato starch modified; PPG-2 cocamide; PPG-1 hydroxyethyl caprylamide; PPG-2 hydroxyethyl cocamide; PPG-2 hydroxyethyl coco/isostearamide; PPG-3 hydroxyethyl soyamide; PPG-14 laureth-60 hexyl dicarbamate; PPG-14 laureth-60 isophoryl dicarbamate; PPG-14 palmeth-60 hexyl dicarbamate; propylene glycol alginate; PVP/decene copolymer; PVP montmorillonite; pyrus cydonia seed; pyrus malus (apple) fiber; rhizobian gum; ricebranamide DEA; ricinoleamide DEA; ricinoleamide MEA; ricinoleamide MIPA; ricinoleamidopropyl betaine; ricinoleic acid/adipic acid/AEEA copolymer; rosa multiflora flower wax; sclerotium gum; sesamide DEA; sesamidopropyl betaine; sodium acrylate/acryloyldimethyl taurate copolymer; sodium acrylates/acrolein copolymer; sodium acrylates/acrylonitrogens copolymer; sodium acrylates copolymer; sodium acrylates crosspolymer; sodium acrylate/sodium acrylamidomethylpropane sulfonate copolymer; sodium acrylates/vinyl isodecanoate crosspolymer; sodium acrylate/vinyl alcohol copolymer; sodium carbomer; sodium carboxymethyl chitin; sodium carboxymethyl dextran; sodium carboxymethyl beta-glucan; sodium carboxymethyl starch; sodium carrageenan; sodium cellulose sulfate; sodium chloride; sodium cyclodextrin sulfate; sodium hydroxypropyl starch phosphate; sodium isooctylene/MA copolymer; sodium magnesium fluorosilicate; sodium oleate; sodium palmitate; sodium palm kernelate; sodium polyacrylate; sodium polyacrylate starch; sodium polyacryloyldimethyl taurate; sodium polygamma-glutamate; sodium polymethacrylate; sodium polystyrene sulfonate; sodium silicoaluminate; sodium starch octenylsuccinate; sodium stearate; sodium stearoxy PG-hydroxyethylcellulose sulfonate; sodium styrene/acrylates copolymer; sodium sulfate; sodium tallowate; sodium tauride acrylates/acrylic acid/acrylonitrogens copolymer; sodium tocopheryl phosphate; solanum tuberosum (potato) starch; soyamide DEA; soyamidopropyl betaine; starch/acrylates/acrylamide copolymer; starch hydroxypropyltrimonium chloride; stearamide AMP; stearamide DEA; stearamide DEA-distearate; stearamide DIBA-stearate; stearamide MEA; stearamide MEA-stearate; stearamide MIPA; stearamidopropyl betaine; steareth-60 cetyl ether; steareth-100/PEG-136/HDI copolymer; stearyl alcohol; stearyl betaine; sterculia urens gum; synthetic fluorphlogopite; tallamide DEA; tallow alcohol; tallowamide DEA; tallowamide MEA; tallowamidopropyl betaine; tallowamidopropyl hydroxysultaine; tallowamine oxide; tallow betaine; tallow dihydroxyethyl betaine; tamarindus indica seed gum; tapioca starch; TEA-alginate; TEA-carbomer; TEA-hydrochloride; trideceth-2 carboxamide MEA; tridecyl alcohol; triethylene glycol dibenzoate; trimethyl pentanol hydroxyethyl ether; triticum vulgare

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(wheat) germ powder; triticum vulgare (wheat) kernel flour; triticum vulgare (wheat) starch; tromethamine acrylates/acrylonitrogens copolymer; tromethamine magnesium aluminum silicate; undecyl alcohol; undecylenamide DEA; undecylenamide MEA; undecylenamidopropyl betaine; welan gum; wheat germamide DEA; wheat germamidopropyl betaine; xanthan gum; yeast beta-glucan; yeast polysaccharides and zea mays (corn) starch.

Product forms

[00119] Acknowledging the many ways topical personal care and pharmaceutical compositions may be used, it is within the scope of the invention that the thickened compositions may have the form of a solution, a cream, an ointment, a lotion, an oil-in-water emulsion, a water-in-oil emulsion, a shampoo, a spray, a gel, a wash, a rinse, an aerosol, a suspension, a paste, a powder, a serum, or a mousse.

[00120] In other examples of the invention, thickened compositions may be used to wash and treat keratinous material such as hair, skin, eyelashes, eyebrows, fingernails, lips, and hairy skin. The compositions of the invention may also take the form of skin-washing compositions, and particularly in the form of solutions or gels for the bath or shower, or of make-up removal products.

[00121] The compositions according to the invention may also take the form of after-shampoo compositions, to be rinsed off or not, for permanents, straightening, waving, dyeing, or bleaching, or the form of rinse compositions to be applied before or after dyeing, bleaching, permanents, straightening, relaxing, waving or even between the two stages of a permanent or straightening process.

[00122] Examples of related compositions are disclosed in U.S. patents 5,599,800; 5,650,166; 5,916,549; and 6,812,192; U.S. patent application 2009/0317432; EP 556,660; 661,037; 661,038; 662,315; 676,194; 796,077; 970,682; 976383; 1,415,654; and 2,067,467; and WO 2005/032506; each of which is incorporated herein its entirety by reference.

[00123] The compositions according to the invention can be detergent compositions such as shampoos, bath gels, and bubble baths. In this mode, the compositions will comprise water as a

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liquid carrier. The surfactant or surfactants that form the washing base may be chosen alone or in blends, from known anionic, amphoteric, or non-ionic surfactants. The quantity and quality of the washing base must be sufficient to impart a satisfactory foaming and/or detergent value to the final composition. The washing base can be from 4% to 50% by weight, preferably from 6% to 35% by weight, and even more preferentially from 8% to 25% by weight of the total weight of the final composition.

[00124] Cosmetic compositions according to the invention may, for example, be used as care and/or sun protection product for the face and/or the body having a consistency ranging from liquid to semiliquid (*e.g.*, milks, creams), and gels, creams, pastes, powders (including compacted powders), and wax-like compositions (*e.g.*, lip balms).

[00125] For compositions intended to protect the hair from UV radiation, suitable product forms include, but not limited to: conditioners, dispersions, emulsions, gels, lotions, mists, mousses, shampoos, and sprays.

[00126] The personal care active includes shampoo, body wash products, shaving cream, hand soap, bubble bath, bath gel, after-shave lotions, creams, moisturizers, sunscreens, liquid soaps, color cosmetics, acid peels, perms, hair color, sunless tanning and conditioners.

[00127] Due to the low pH of these topical compositions, they may be expected provide a skin exfoliation effect (also known as keratolysis). As such, these acidic formulations find use in treating wrinkles and dry skin. Other skin and scalp conditions that can be treated by these thickened, low pH compositions also are contemplated, for example, the use of thickened salicylic acid formulations for the treatment of various warts, corns, and calluses. Examples of wart-removal compositions include the following, each of which is incorporated herein its entirety by reference: U.S. patents 5,962,011 and 7,655,668; US patent application 2007/0280972; EP 1,002,530; and WO 2009/085890. Examples of skin lightening compositions and age-spot compositions include the following, each of which is incorporated herein its entirety by reference: U.S. 5,747,051; U.S. patent application 2008/0214669; EP 1028723; and WO 2004/073745.

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[00128] The following examples are presented to illustrate specific embodiments of the present compositions and methods. These examples should not be interpreted as limitations upon the scope of the invention.

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EXAMPLES

Example 1: Ascorbic acid and glycolic acid gels

[00129] Two formulations were prepared containing 10% ascorbic acid or 10% glycolic acid in water with 5% lightly- to moderately-crosslinked PVP (Table 1). Neither composition phase separated or coagulated, but rather both were smooth, low pH gels as indicated in Table 1.

[00130] Table 1: Low pH glycolic acid and ascorbic acid gels of Example 1.

active	liquid carrier	lightly- to moderately-crosslinked PVP	initial pH[†]	viscosity[*]
10% ascorbic acid	water	5%	3.88	23,000
10% glycolic acid	water	5%	3.92	13,500

[†]pH was measured at 25°C.

[*]Viscosity was measured using a Brookfield LVT viscometer with spindle T-E at 10 rpm and 25°C.

Examples 2–6: Thickened acidic systems having lightly- to moderately-crosslinked PVP

[00131] Five low pH compositions of the invention were made by blending between 4.5%–6.0% lightly- to moderately-crosslinked PVP, a personal care acid, and at least one liquid carrier (Table 2). The five preparations were smooth gels having a pH less than 3.0 and viscosities of 15,000 cP or more.

[00132] Thickened acidic systems such as these may represent stand-alone formulations. Alternatively, their pH and viscosity stability allows them to be treated as sub-formulations to be prepared in advance, and then to be added to other ingredients as necessary.

[00133] Table 2: Thickened acidic systems of Examples 2-6

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ex.	ingredients	addition level (% w/w)	appearance	pH†	viscosity*
2	lightly- to moderately-crosslinked PVP	4.5	gel	1.68	15,000
	glycolic acid, (70% solution)	43.0			
	deionized water	52.5			
	total	100.0			
3	lightly- to moderately-crosslinked PVP	6.0	gel	2.9	22,000
	salicylic acid, USP	10.0			
	SD alcohol 40	84.0			
	total	100.0			
4	lightly- to moderately-crosslinked PVP	4.5	gel	1.32	30,000
	glycolic acid, (70% solution)	71.0			
	deionized water	24.5			
	total	100.			
5	lightly- to moderately-crosslinked PVP	4.5	gel	1.35	35,000
	glycolic acid, (70% solution)	71.0			
	deionized water	14.5			
	SD alcohol 40	10.0			
	total	100.0			
6	lightly- to moderately-crosslinked PVP	4.5	gel	1.45	37,000
	glycolic acid (70% solution)	71.0			
	deionized water	4.5			
	SD alcohol 40	20.0			
	total	100.0			

†pH was measured at 25°C.

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*Viscosity measured using a Brookfield LVT viscometer with spindle T-C at 10 rpm and 25°C.

Example 7: Acne gel preparation

[00134] An acne gel preparation was made containing two active ingredients, 2% salicylic acid and 5% glycolic acid (Table 3). First, salicylic acid was dissolved in ethanol, to which water and glycolic then were added with mixing. The pH of this sub-formulation was adjusted to 4.2 using ammonium hydroxide solution. Then, lightly- to moderately crosslinked PVP was added followed by homogenization. To this thickened gel two emollients (Ceraphyl® 41 and Lubrajel® Oil) were added.

[00135] The preparation described above appeared as a gel, and the measured pH was 4. The viscosity, measured by a Brookfield RVT viscometer using spindle T-C at 10 rpm and 25°C was 24,000 cP.

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[00136] Table 3: Acne gel formulation of Example 7.

ingredient		addition level (% w/w)
Phase A		
water		38.9
salicylic acid		2.0
glycolic acid (70%)		7.2
ammonium hydroxide solution (28%–30%)		1.4
	total	49.5
Phase B		
ethanol		40.0
lightly- to moderately-crosslinked PVP		5.0
	total	45.0
Phase C		
Ceraphyl® 41		3.0
Lubrajel® Oil		2.5
	total	5.5
	grand total	**100.0**

Example 8: Stability of acne gel preparation of Example 7

[00137] The acne gel of Example 7 was placed on stability testing at 5°C, 25°C, and 45°C to determine if viscosity or pH changed over time or after freeze / thaw cycles. Viscosity was measured using a Brookfield RVT viscometer with an T-C spindle at 10 rpm. Freeze / thaw cycles were defined as freezing overnight at -15°C, followed by next morning thaw at 25°C until the acne gel reached 25°C.

[00138] Measured viscosities at 5°C and 25°C were essentially constant over the 12 week test period (Figure 1). Storage at 45°C produced slightly increased viscosity, from an initial value of 24,000 cP to 32,000 cP.

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[00139] Like viscosity, pH was essentially constant over the 12 week stability period. At 5°C storage the acne gel pH remained essentially constant, while at 25°C and 45°C a small increase of about 0.2 unit was recorded (Figure 2).

Example 9: Crème brûlée skin renewal treatment formulation

[00140] A renewal treatment for dry, slack, rough, and/or wrinkled skin was prepared containing the ingredients and amounts shown in Table 4. This formula was made by preparing Phase A with moderate mixing, followed by separate preparation of Phase B, adjusting the pH with ammonium hydroxide to a pH of 3.8–4.2. Then, Phase B was mixed in to Phase A, and the resulting blend was heated to 75°C. In a different beaker, the ingredients of Phase C were combined and heated to 75°C. Then, Phase A-B and Phase C were combined and mixed for 5 minutes. The combination then was homogenized to 65°C–70°C, followed by mixing. After this step, Phase D was prepared and added to the combination of Phases A-B-C. When the final product cooled to 40°C, mixing was stopped, and allowed to thicken overnight.

[00141] The crème brûlée skin renewal treatment formula had a final appearance of a smooth, off-white cream / gel. The viscosity, measured by a Brookfield RVT viscometer using spindle T-C at 10 rpm, was 40,000 cP – 42,000 cP.

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[00142] Table 4: Crème brûlée skin renewal formulation of Example 9

ingredient		addition level (% w/w)
Phase A		
deionized water		36.6
lightly- to moderately-crosslinked PVP		3.5
propylene Glycol		2.0
disodium EDTA		0.1
	total	42.2
Phase B		
deionized water		20.0
glycolic acid (70% active solution)		11.4
citric acid, anhydrous USP		2.0
ammonium hydroxide (28% active solution)		2.8
	total	36.2
Phase C		
dicetyl phosphate, ceteth-10 phosphate		3.5
cetearyl alcohol		2.5
isodecyl neopentanoate		2.5
isocetyl stearate		2.0
decyl oleate		2.25
shea butter		0.75
dimethicone		0.75
	total	14.25
Phase D		
disodium lauriminodipropionate tocopheryl phosphates		0.75
diazolidinyl urea and iodopropynyl butylcarbamate		0.6
Collaxyl		2.0

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Orsirtine		1.0
Achromaxyl IS		3.0
	total	7.35
	grand total	**100.0**

Example 10: Reduced sting with tartaric acid solution

[00143] An independent, third-party clinical laboratory evaluated sting as a consumer perception of irritation for two formulations. The first formula was a 0.5% tartaric acid aqueous solution, and the second formula was an example of the invention, being identical to the first except it additionally contained 5% lightly- to moderately-crosslinked PVP. The facial discomfort assay test was conducted as a double-blind, crossover study. The formulas were applied to the faces of ten healthy, adult woman aged 21–67 previously tested and known to exhibit skin sensitivity to lactic acid. Prior to testing the abovedescribed two formulas, the volunteers' faces were washed with a standard, commercial beauty preparation, then gently patted dry. Approximately 1.0 mL of the two formulas was separately dispensed onto cotton swabs and liberally spread in smooth motions across the upper cheek area. Volunteers were instructed to record the discomfort/sting intensity of the two formulas after 2.5 and 5 minutes using the scale of Table 5. Additionally, the volunteers recorded all physical sensations. Relevant discomfort responses include: burning, stinging, tingling, itching, drying, smarting, prickly, and warm/hot. The evaluation method followed that described in Frosch, P.J. and Kligman, A.M., "A method for appraising the stinging capacity of topically applied substances," *J. Soc Cos Chem*, 28, p. 197-209 (1977), which hereby is incorporated in its entirety by reference.

[00144] In its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. The mean numerical scale rating for the first formula was 0.68, and the mean numerical scale rating for the second formula (with lightly- to moderately-crosslinked PVP) was 0.18 (Table 6). Seven of the women did not sense any discomfort or irritation from the second formula (with lightly- to moderately-crosslinked PVP).

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Table 5: Discomfort/sting intensity scale used in Example 10

numerical scale rating	volunteer perception
0	none
0.5	barely perceptible
1.0	slightly perceptible
1.5	definitely perceptible
2.0	moderately perceptible
2.5	dramatically perceptible
3.0	severely perceptible

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[00145] Table 6: Numerical scale rating results for the independent, third-part evaluation of Example 10.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	1.0	0.5	0	0	0
2	0.5	0.5	0.5	0	0	0
3	1.0	0	0.5	0.5	0	0.25
4	0	1.0	0.5	0	0	0
5	1.0	0	0.5	1.0	0.5	0.75
6	1.0	1.0	1.0	0	0	0
7	1.0	0.5	0.75	0	0	0
8	1.0	1.0	1.0	0	1.5	0.75
9	1.0	0	0.5	0	0	0
10	1.0	1.0	1.0	0	0	0
		mean:	**0.68**			**0.18**
		standard deviation:	**0.24**			**0.32**

Example 11: Reduced sting with salicylic acid solution

[00146] Example 10 was repeated except salicylic acid replaced tartaric acid in both formula 1, the control (without lightly- to moderately-crosslinked PVP) and formula 2, the composition of the invention (with lightly- to moderately-crosslinked PVP). The concentration of salicylic acid in Example 11 was 0.5% (w/w) in both solutions.

[00147] In its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. Less discomfort/sting and a more uniform volunteer perception was recorded by the volunteers for the

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formula of the example containing lightly- to moderately-crosslinked PVP (Table 7). Nine women did not sense any discomfort or irritation from the second formula (example of the invention).

[00148] Table 7: Numerical scale rating results for the independent, third-part evaluation of Example 11.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	0	0	0	0	0
2	1.0	1.0	1.0	0	0	0
3	1.0	1.0	1.0	0	0	0
4	1.0	1.0	1.0	0	0	0
5	0	0	0	0.5	0.5	0.5
6	1.5	1.0	1.25	0	0	0
7	1.0	0	0.5	0	0	0
8	1.0	1.0	1.0	0	0	0
9	1.0	1.0	1.0	0	0	0
10	0	1.0	0.5	0.5	0	0
		mean:	**0.72**			**0.075**
		standard deviation:	**0.45**			**0.16**

Example 12: Reduced sting with salicylic acid solution

[00149] Example 11 was repeated except a 2.0% salicylic acid solution replaced the 0.5% salicylic acid solution in both the control (without lightly- to moderately-crosslinked PVP) and the composition of the invention (with lightly- to moderately-crosslinked PVP).

[00150] Again, in its written report, the independent, third-party laboratory concluded that formula 1 (without lightly- to moderately-crosslinked PVP) may be considered as stinging, while formula 2 (with lightly- to moderately-crosslinked PVP) may be considered as non-stinging. Less

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discomfort/sting and a more uniform volunteer perception was recorded by the volunteers for the formula of the example containing lightly- to moderately-crosslinked PVP (Table 8).

[00151] Table 8: Numerical scale rating results for the independent, third-part evaluation of Example 12.

volunteer	formula 1: without lightly- to moderately-crosslinked PVP			formula 2: with lightly- to moderately-crosslinked PVP		
	2.5 min	5.0 min	mean	2.5 min	5.0 min	mean
1	0	1.0	0.5	0	0	0
2	1.0	1.5	1.25	0	0	0
3	0	0	0	0.5	0	0.25
4	0	0	0	0	0.5	0.25
5	1.0	1.0	1.0	0	0.5	0.25
6	0.5	1.0	0.75	0	0	0
7	0	0	0	0	1.0	0.5
8	1.5	1.0	1.25	0	1.0	0.5
9	1.0	1.0	1.0	0	0	0
10	0	0	0	0.5	0.5	0.5
		mean:	**0.58**			**0.22**
		standard deviation:	**0.54**			**0.22**

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What is claimed is:

1. A composition comprising at least: (A) one personal care acid at 0.5% (% w/w) addition level or more, or one pharmaceutical acid at 0.5% (% w/w) addition level or more, and (B) lightly- to moderately-crosslinked PVP.

2. The composition of claim 1 wherein said addition level of either said personal care acid or said pharmaceutical acid is 1% or more.

3. The composition of claim 1 that has a pH of about 4 or lower.

4. The composition of claim 3 wherein said pH is about 2 or lower.

5. The composition of claim 1 that is a prescriptive or non-prescriptive composition.

6. The composition of claim 5 wherein said non-prescriptive composition is a personal care composition.

7. The composition of claim 1 that is applied on the skin, hair, scalp, foot, or lip of a mammal.

8. The composition of claim 5 that is an anti-aging composition, a composition for skin blemishes, a smoothing composition, a moisturizing composition, a skin firming composition, a skin lightening composition, an age-spot composition, a shampoo, or a cream for use around the eyes or mouth.

9. The composition of claim 1 wherein said personal care acid or pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N*'-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid

(procysteine), pyruvic acid, trichlorosacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

10. The composition of claim 9 wherein hydroxy acid is selected from the group consisting of: alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

11. The composition of claim 9 wherein the said alpha hydroxy acid is selected from the group consisting of: alpha hydroxyethanoic acid, alpha hydroxyoctanoic acid, alpha hydroxycaprylic acid, ascorbic acid, adipic acid, caprylic acid, capric acid, glycolic acid, lactic acid, lauric acid, mandelic acid, mixed fruit acids, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, ricinoleic acid, oleic acid, tartaric acid, elaidic acid, erucic acid, and blends thereof.

12. The composition of claim 9 wherein the said beta hydroxy acid is selected from the group consisting of: beta hydroxybutanoic acid, tropic acid, trethocanic acid, salicylic acid, 5-(*n*-octanoyl) salicylic acid, and blends thereof.

13. The composition of claim 9 wherein said alpha and beta hydroxy acid is selected from the group of consisting of: citric acid, malic acid, tartaric acid, and blends thereof.

14. The composition of claim 9 wherein said polyhydroxy acid is selected from the group consisting of: gluconolactone acid, gactobionic acid, and blends thereof.

15. The composition of claim 1 having from about 0.1% to about 10% lightly- to moderately-crosslinked PVP.

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16. The composition of claim 1 having the form of: a solution, a cream, an ointment, a lotion, an oil-in-water emulsion, a water-in-oil emulsion, a shampoo, a spray, a gel, an aerosol, a suspension, a paste, a powder, a serum, or a mousse.

17. The composition of claim 1 that further comprises at least one additional ingredient selected from the group consisting of: active ingredients, emollients, liquid carriers, surfactants, emulsifiers, rheology modifiers, lubricants, diluents, humectants, anti-oxidants, preservatives, antibiotics, and blends thereof.

18. The composition of claim 17 further wherein said liquid carrier is selected from the group consisting of: water, alcohols, oils, esters, and blends thereof.

19. The composition of claim 1 having enhanced viscosity, enhanced viscosity stability, or enhanced viscosity and pH stability compared to the same composition without said lightly- to moderately-crosslinked PVP.

20. The composition of claim 1 having a Brookfield viscosity at 10 rpm of about 7,000 cP or more.

21. The use of a composition comprising at least: (A) one personal care acid at 0.5% addition level or more or one pharmaceutical acid at 0.5% addition level or more, and (B) lightly- to moderately-crosslinked PVP to deliver either said acid to the skin, scalp, foot, or lip of a mammal.

22. The use of claim 21 wherein said personal care acid or said pharmaceutical acid is selected from the group consisting of: hydroxy acids, aminosulphonic compounds, (*N*-2-hydroxyethyl) piperazine-*N*'-2-ethanesulphonic acid; 2-oxothiazoline-4-carboxylic acid (procysteine), pyruvic acid, trichloroacetic acid, editronic acid, dioic acid, azelaic acid, their salts, esters and derivatives, and blends thereof.

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23. The use of claim 22 wherein said hydroxy acid is selected from the group consisting of: alpha hydroxy acids, beta hydroxy acids, alpha and beta hydroxy acids, polyhydroxy acids, their salts, esters, derivatives, and blends thereof.

24. The use of claim 21 wherein said addition level of either said personal care acid or said pharmaceutical acid is 1% or more.

25. The use of lightly- to moderately-crosslinked PVP in combination with at least one personal care acid or at least one pharmaceutical acid to reduce irritation, stinging, burning, tingling, itching, drying, smarting, prickly, and/or warm/hot perception on the skin, scalp, foot, or lip compared to the same composition not having said lightly- to moderately-crosslinked PVP.

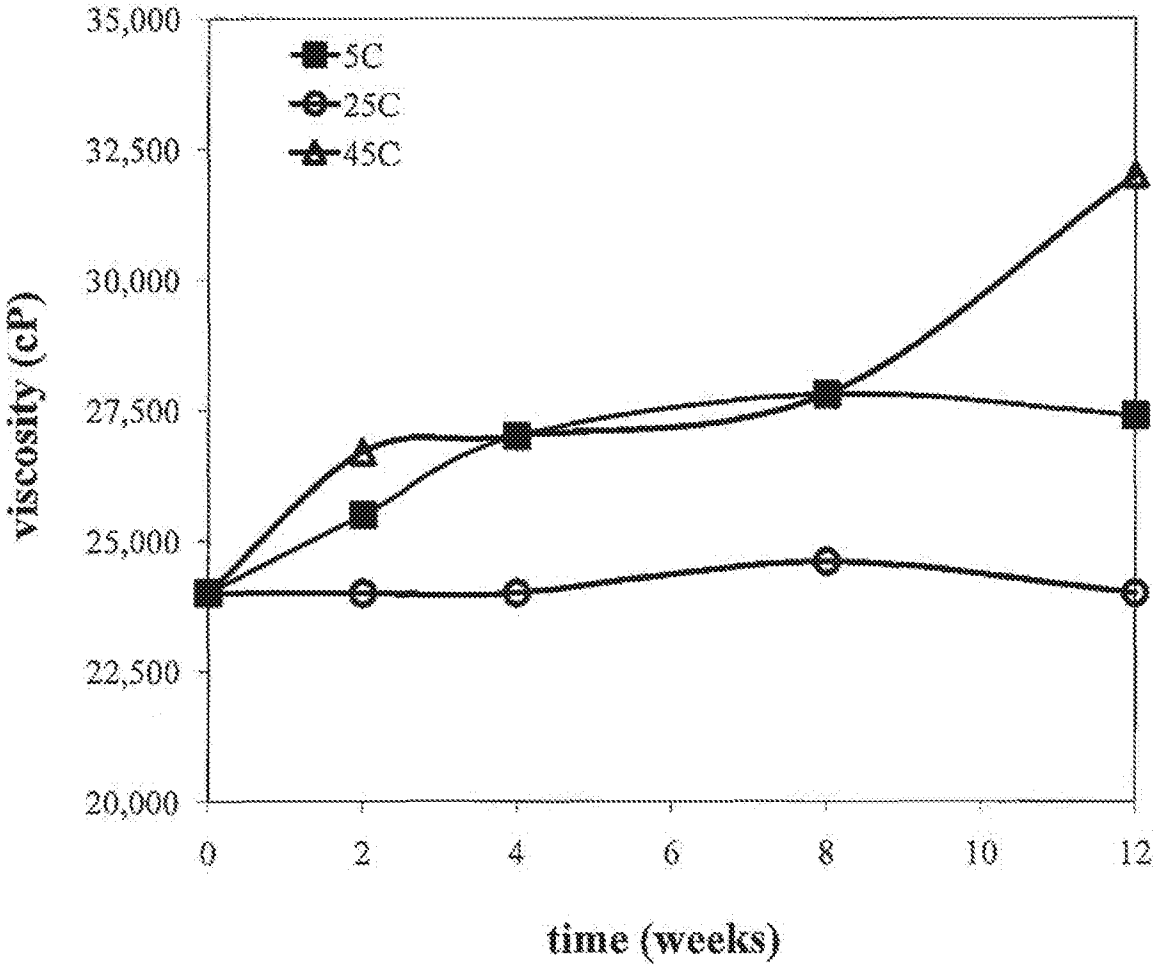

Fig: 1

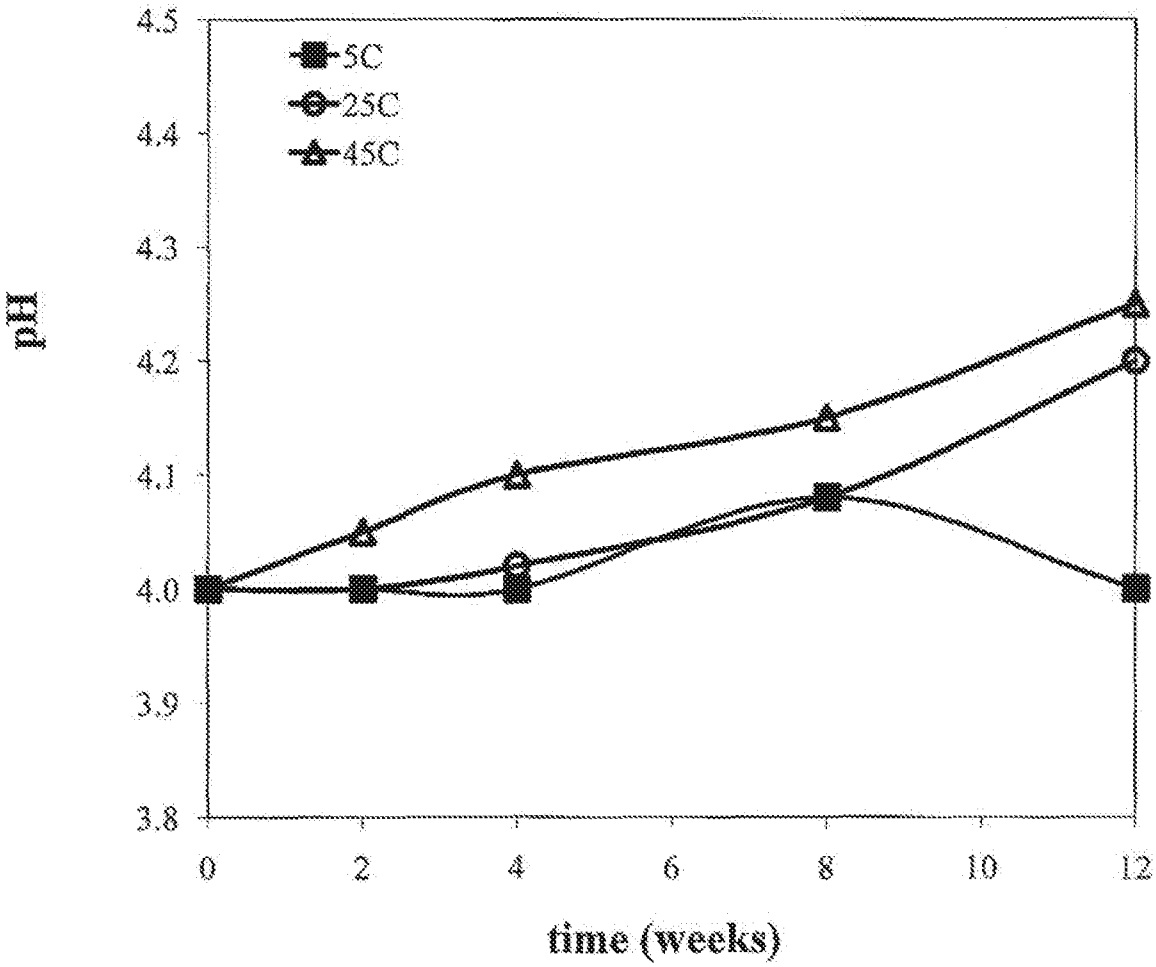

Fig: 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26978

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 8/02 (2010.01)
USPC - 424/401
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8) - A61K 8/02 (2010.01)
USPC - 424/401

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/401,400,59,65,66,68 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: lightly to moderately crosslinked PVP, hydroxy acid, pH, polyhydroxy, gluconolactone, gactobionic, irritation, viscosity, Brookfield

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,312,714 B1 (Prosise et al.) 6 November 2001 (06.11.2001), abstract, col 1, ln 13-50; col 4, ln 36-45; col 5, ln 27-30; col 6, ln 37-60; col 7, ln 10-14; col 12, ln 10-15; col 15, ln 39-41;	1-13, 15-25 --- 14
Y	US 2008/0113037 A1 (Green et al.) 15 May 2008 (15.05.2008), abstract, para [0011], [0012], [0045]	14
A	US 5,736,128 A (Chaudhuri et al.) 7 April 1998 (07.04.1998), entire disclosure	1-25
A	US 5,073,614 A (Shih et al.), 17 December 1991 (17.12.1991), entire disclosure	1-25
A	US 2004/0234491 A1 (Braustgam et al.) 25 November 2004 (25.11.2004), entire disclosure, esp: para [0046]	25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2010 (17.04.2010)	28 APR 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Electronic Patent Application Fee Transmittal

Application Number:	14885805
Filing Date:	16-Oct-2015
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	19107 DIV (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	24954402
Application Number:	14885805
International Application Number:	
Confirmation Number:	9004
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	19107 DIV (AP)
Receipt Date:	18-FEB-2016
Filing Date:	16-OCT-2015
Time Stamp:	16:29:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	3430
Deposit Account	010885
Authorized User	WINE, LAURA L.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	19107DIV_IDS_Filed_021816.pdf	84506 2a7079c425f7c6c24cbffd2db0c3c3eb0928f033	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
2		19107DIV_References_A.pdf	10204450 d04d81da513298f1f5389eaf9479a5ffd3520e72	yes	46

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Other Reference-Patent/App/Search documents	1	10
Non Patent Literature	11	36
Non Patent Literature	37	46

Warnings:					
Information:					
3		19107DIV_References_B.pdf	18425658 3eeccb50fe33a703d851c29c238c991a2c4ca54c	yes	147

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Foreign Reference	1	64
Foreign Reference	65	98
Foreign Reference	99	147

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30657 10a86af95a610fc6c8cfee67d9fee68ff40c20bd	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	28745271

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/885,805	Filing Date 10/16/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	02/18/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 12	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/DEBORAH PORTER/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

51957 7590 03/07/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/07/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

Office Action Summary	Application No. 14/885,805	Applicant(s) WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-12* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-5 and 7-9* is/are rejected.

8)☒ Claim(s) *6 and 10-12* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *18Feb16*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-12 are presented for examination.

Applicant's Amendment and Information Disclosure Statement (IDS) filed February 18, 2016 have each been entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08A (three pages total), the Examiner has considered the cited references.

Claims 1-12 are pending and under examination. Claims 11-12 are newly added. Claims 1, 5-7, 9 and 10 are amended.

Applicant's arguments, filed February 18, 2016, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Applicant's Arguments and Declaration Filed February 18, 2016

In the submission filed February 18, 2016, Applicant provides various remarks directed to the obviousness rejections of record under 35 U.S.C. §103 (Reply, p.5-8), as well as a declaration of inventor Kevin S. Warner (hereinafter "the Warner Declaration") executed under 37 C.F.R. §1.132 in support of nonobviousness.

Applicant's most pertinent argument set forth in the record with regard to the nonobviousness of the claimed invention appears to be the data provided in the Warner Declaration (p.2, para.[4]-p.3, para.[10]). In the Warner Declaration, the Declarant states that he was involved with the development of a topical dapsone formulation with greater dapsone concentration (7.5% w/w) than the conventional 5.0% w/w ACZONE gel formulation (p.2, para.[4]). In order to increase the dapsone concentration from 5.0% w/w to 7.5% w/w as desired, the Warner Declaration states that a corresponding increase in diethylene glycol monoethyl ether (DGME) from its 25% w/w amount typically found in the 5.0% w/w ACZONE gel was necessary to solubilize dapsone in the formulation (p.2, para.[5]). A screening of various thickening

agents for use in the dapsone formulation identified two specific agents selected for their ability to thicken the proposed dapsone formulation: (i) CARBOPOL 980 (the same thickener agent employed in the closest prior art to Garrett) and (ii) SEPINEO P 600 (which is an acrylamide/sodium acryloyldimethyl taurate copolymer as recited for use in the instantly claimed formulation).

Experimental studies described in the Warner Declaration demonstrated that the use of 7.5% w/w dapsone with 40% w/w DGME and CARBOPOL 980 "showed undesired polymer aggregates" at this high concentration of DGME, but that "[t]his aggregation was not observed with [7.5% w/w dapsone] formulations containing SEPINEO P 600 at 40% DGME" (p.2-3, para.[7]). The Warner Declaration further notes that this incompatibility of CARBOPOL 980 with 40% DGME was unexpected as "CARBOPOL 980 is compatible at concentrations of 25% DGME" (p.3, para.[7]). Further comparisons of dapsone particle size of a gel formulation comprising 7.5% w/w dapsone, 30% w/w DGME and 4% w/w SEPINEO P 600 with a 7.5% w/w dapsone gel containing either 25% or 30% w/w DGME and 1% w/w CARBOPOL 980 were made, noting that the 7.5% w/w dapsone gel formulation using SEPINEO P 600 effectively reduced recrystallized dapsone particle size as compared to either CARBOPOL 980 formulation (Warner Declaration, p.5, Tables 1-2). Note that the quantity of CARBOPOL 980 used in the comparative formulations is lower than that of SEPINEO P 600, but it is understand from the Warner Declaration that the use of a greater quantity of CARBOPOL 980 would have further contributed to the polymer aggregation known to occur between higher concentrations of DGME (as used in the comparative formulations) and CARBOPOL 980.

The Warner Declaration, therefore, provides clear evidence that the improved properties of Applicant's claimed 7.5% w/w dapsone formulation (specifically, the reduction in undesirable polymer aggregates, as well as the reduction in dapsone particle size, thereby providing a smoother, less gritty gel formulation with reduced recrystallization of dapsone) yields directly from the selection of the acrylamide/sodium acryloyldimethyl taurate copolymer as the polymeric thickener of the formulation. As the proffered data appears to be reasonably representative of, and commensurate in scope with, the instantly claimed 7.5% w/w dapsone formulation as stipulated by MPEP §716.02(d), and further in view of the fact that the comparative dapsone formulations employed the same thickening agent used by the

closest prior art to Garrett in the same quantity suggested by this prior art reference (thereby constituting a reasonable comparison of the instantly claimed formulation with that of the closest prior art; MPEP §716.02(e)), the Warner Declaration appears to be probative of unexpected properties of the claimed formulation.

Accordingly, the obviousness rejections under 35 U.S.C. §103 (as well as the nonstatutory obviousness-type double patenting rejections over U.S. Patent No. 8,586,010 and U.S. Patent Application No. 14/063,841) are withdrawn in light of the evidence.

Objection to the Claims (New Grounds of Objection)

In view of the evidence and the withdrawal of the above-noted rejections, it is noted that instant claims 6 and 10-12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112(a) (Pre-AIA First Paragraph), Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-9 remain rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any dermatological condition, because the specification does not enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth at p.2-5 of the previous Office Action dated November 18, 2015, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

In reply, Applicant opines "that all of the pending claims comply with the enablement requirement" in view of the fact that "[t]he disclosure of the present application clearly states that compositions described in the application are effective in treating dermatological conditions, including, but not limited to those recited in [c]laims 5 and 9" (Reply, p.4). Applicant further alleges that "[s]ince the disorders being treated by the claimed methods are disclosed in the application as specifically tied to the compositions and formulations therein, sufficient information regarding the subject matter of the claims exists so as to enable one skilled in the art to make and use the claimed methods" (Reply, p.5).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's remarks fail to address the evidence cited in support of the rejection's position that the instant claims, directed to methods for treating any dermatological condition (including, but clearly not limited to, those recited in instant claims 5 and 9), are not adequately enabled for the treatment of any such dermatological condition aside from acne vulgaris or rosacea. Garrett (WO 2009/108147; 2009) and Ahluwahlia et al. (WO 2011/014627; 2011) were cited as evidence of the state of the art with regard to topical dapsone therapy, each documenting the efficacy of topical dapsone preparations in the treatment of acne vulgaris and rosacea only. Neither Garrett nor Ahluwahlia et al., however, provide any evidentiary support to corroborate Applicant's assertions that topical dapsone therapy was known to be useful or effective for the treatment of the various specific dermatological conditions claimed (e.g., atopic dermatitis, bed sores, keratosis pilaris, nodular prurigo, sebaceous cysts, etc.), let alone any or all numerous and varied dermatological conditions known (or unknown) in the art as of the effective filing date of the claimed invention (e.g., melanoma, squamous cell carcinoma, psoriasis, ichthyosis, Stevens-Johnson syndrome, tinea pedis, keloid formation, etc.). Applicant's remarks provide nothing more than speculative and conclusory statements that the instant claims are enabled for the entire breadth of

dermatological conditions known in the art, but points to nothing in Garrett or Ahluwahlia et al. (or even any extraneous evidence in support of his position) that would bolster his allegation that topical dapsone therapy would have been effective for more than just the treatment of acne vulgaris or rosacea.

It was additionally noted that a diligent search of the prior and contemporaneous art at the time of the effective filing date of the claimed invention did not reveal any clear teachings supporting the use of topical dapsone therapy for the treatment of any possible type of dermatological condition known in the art as instantly claimed (aside from acne vulgaris or rosacea). McGeer et al. (U.S. Patent No. 5,532,219; 1996) was previously cited in further support of this position, in which other therapeutic uses of dapsone therapy were suggested, but of which none specifically related to other dermatologic uses of topical dapsone therapy (aside from acne vulgaris or rosacea). The state of the art, therefore, as of the effective filing date of the claimed invention did not clearly and unequivocally recognize the usefulness of topical dapsone therapy for dermatological applications outside of the treatment of acne vulgaris or rosacea as established by Garrett and Ahluwahlia et al. Applicant, therefore, cannot rely upon the state of the art as of the effective filing date of the claimed invention to enable his claimed topical dapsone formulation for the treatment of any or all dermatological conditions known (or unknown) in the art as of the effective filing date of the claimed invention.

The skilled artisan, therefore, has nothing else to rely upon but Applicant's own specification to bridge this clear gap between the knowledge accepted in the art as of the effective filing date of the claimed invention and the asserted applications of Applicant's claimed topical dapsone therapy. This lack of knowledge in the art regarding the effective use of topical dapsone therapy for the treatment of any or all dermatological conditions (including, but not limited to, those recited in instant claims 5 and 9) is not remedied by Applicant's own specification. Applicant's working examples fail to demonstrate the ability of the claimed topical dapsone preparations to treat any type of dermatological condition (including those specific conditions claimed) in a patient in need thereof and, therefore, fail to provide the necessary enabling guidance that is absent from the state of the art. Applicant's proffered working examples are limited to specific topical preparations of dapsone and do not demonstrate the efficacy of such formulations in the treatment of any type of dermatological condition (including any or all of those specific

conditions instantly claimed). The working examples, therefore, fail to provide any evidentiary basis to conclude that Applicant's claimed method of administering the recited topical dapsone therapy was effective to treat any or all types of dermatological conditions. Accordingly, it remains that the disclosure and supporting examples provided in the present specification, coupled with the nascent state of the art at the time of the invention with regard to topical dapsone therapy for the treatment of any or all dermatological conditions, fails to adequately enable the full scope of embodiments presently claimed. The rejection stands.

For these reasons *supra*, rejection of claims 1-5 and 7-9 is proper.

Conclusion

Rejection of claims 1-5 and 7-9 is proper.

Claims 6 and 10-12 are objected to for depending from a rejected base claim.

No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

March 2, 2016

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9616	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L2	25262	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L3	258942	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L4	20	1 and 2 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L5	20	4 and (water aqueous (purified adj water))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L6	27135	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L7	20	1 and 3 and 6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L8	0	7 not 5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:30
L9	63	1 and 2 and (water aqueous (purified adj water)) and (methyl adj2 paraben)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:31
L10	58	9 and (acne (acne adj2 vulgaris))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:31
L11	8	4 and (methyl adj2 paraben)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:31
L12	36	10 and (@pd<="20121120" @ad<="20121120")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:31

L13	8	9 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/03/02 10:31
L14	60	(warner-kevin$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L15	19	(parashar-ajay$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L16	6	(swaminathan-vijaya$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L17	5	(bhatt-varsha$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L18	4227	(allergan$).as. (allergan$).aanm. (allergan$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L19	76	14 15 16 17	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L20	6	19 and 1	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:33
L21	4227	(allergan$).as. (allergan$).aanm. (allergan$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:36
L22	71	21 and 1	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:36
L23	6	22 and 3	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:36
L24	3	23 not 20	US-PGPUB; USPAT; USOCR	OR	ON	2016/03/02 10:36

EAST Search History (Interference)

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3/2/2016 10:38:24 AM
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PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14885805
Filing Date	2015-10-16
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107-US-DIV-AP

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5863560		1999-01-26	David Osborne	
	2	6060085		2000-05-09	David Osborne	
	3	6620435		2003-09-16	David Osborne	
	4	7531694		2009-05-12	Villa, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060204526		2006-09-14	Lathrop et al	
	2	20100029781		2010-02-04	Jerome A. Morris	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LARD/

/Leslie A. Royds Draper/ (03/01/2016)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Application Number	14885805
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Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107-US-DIV-AP

	3	20100130613		2010-05-27	DRENO	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009-108147	WO		2009-09-03	QLT USA, INC.		☐
	2	WO2010105052	WO	A1	2010-09-16	ISP INVESTMENTS INC.		☐
	3	WO2011-014627	WO		2011-02-03	Allergan, Inc.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	DRAELOS, ZOE D. ET AL., Two Randomized Studies Demonstrate The Efficacy and Safety Of Dapsone Gel, 5% For The Treatment Of Acne Vulgaris, Journal Of American Academy Of Dermatology, 03/2007, 26 Pages, 56, US	☐
	2	Lubrizol (Online). "Viscosity of CARBOPOL Polymers in Aqueous Systems". (Retrieved 2014-03-18). Retrieved from the Internet:<URL:http://www.lubrizol.com/Life-Science/Documents/Pharmaceutical/Technical-Data-Sheets/TDS-730-Viscosity-Carbopol-in-Aqueous-Systems.pdf>.	☐
	3	Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority, or the Declaration, International Application No. PCT/US2013/070613, International Filing Date, November 18, 2013, Date of Mailing February 12, 2014	☐

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/Leslie A. Royds Draper/ (03/01/2016)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14885805
Filing Date	2015-10-16
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107-US-DIV-AP

EXAMINER SIGNATURE			
Examiner Signature	/Leslie A. Royds Draper/ (03/01/2016)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LARD/

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search (PALM Database, eDAN, EAST)	11/11/15	LARD
EAST Search (See Attached Search History)	11/11/15	LARD
Updated Inventor Search (PALM Database, eDAN, EAST)	03/02/16	LARD
Updated EAST Search (See Attached Search History)	03/02/16	LARD
Review Searches in Parent US Application No.14/082,955	03/02/16	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	02 March 2016

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	14885805	Filing Date	2015-10-16	Docket Number (if applicable)	19107 DIV (AP)	Art Unit	1629
First Named Inventor	Kevin S. Warner			Examiner Name	Draper, Leslie A. Royds		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, to any international application that does not comply with the requirements of 35 U.S.C. 371, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV.

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 010885

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (07-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/LAURA L. WINE/	Date (YYYY-MM-DD)	2016-09-07
Name	LAURA L. WINE	Registration Number	68681

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kevin S. Warner, et al.	)	Group Art Unit: 1629
Serial No.:	14/885,805	)	Examiner: Draper, Leslie A. Royds
Filed:	October 16, 2015	)	Conf. No.: 9004
For:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF	)	

RESPONSE TO FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

This is filed in response to a Final Office Action mailed on March 7, 2015. Please amend the above referenced patent application as follows. Authorization is hereby given to charge any fee required for the filing of this paper, to Deposit Account No. 01-0885.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the **listing of claims** which begin on page 12 of this paper.

Remarks begin on page 14 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend paragraph **[009]** as shown below:

[009] Use of topical compositions of dapsone can be problematic. Topical compositions may act as drying agents for the skin. They remove essential oils and natural skin softeners from the skin thus causing it to be dry, itch and crack. Inclusion of ~~exogeneous~~ exogenous skin emollients, oils and the like, however, causes phase separation and precipitation of dapsone. Use of typical emulsifiers does not solve the dapsone precipitation owing to the lowered dapsone solubility and conflicting physical characteristics of the phases of the resulting composition. In particular, topical compositions including dapsone and methods are needed that would, for example, exhibit improved effectiveness, reduced side effects, or both, when used in a particular patient with a skin condition. Such improved topical compositions including dapsone and methods of their uses are also needed to improve treatment of patients with acne or suspected acne. The present dapsone and dapsone/adapalene compositions can be useful for treating a variety of dermatological conditions. Some useful compositions include dapsone and/or adapalene in a polymeric viscosity builder. Some compositions can be adjusted to optimize the dermal delivery profile of dapsone to effectively treat dermatological conditions and improve the efficiency of pharmaceutical products applied to the skin. Diethylene glycol monoethyl ether is a solubilizer for dapsone, thereby allowing compositions to be prepared with increased solubilized concentrations of dapsone. As a result, the compositions described herein are effective in treating dermatological conditions in a subject in need thereof.

Please amend paragraph **[018]** as shown below:

[018] Some embodiments include compositions and products for treatment of skin conditions and methods of treating skin conditions. The term "skin condition" as used herein encompasses human and animal conditions, disorders, or diseases affecting skin.

Such skin conditions include, but are not limited to, conditions involving skin inflammation, conditions involving sebaceous glands and hair follicles, conditions characterized by acneiform symptoms, and conditions involving skin dryness, skin thickening, skin scaling or skin flaking. Skin conditions that can be treated using some compositions, products and methods described herein include, but are not limited to, acne, rosacea, folliculitis, perioral dermatitis, photodamage, skin aging, psoriasis, ~~ichtiosis,~~ ichthyosis, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis ~~piralis,~~ pilaris, scars, including surgical and acne scars, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, ~~pruritis,~~ pruritus, lichen planus, nodular prurigo, eczema, and miliaria.

Please amend paragraph **[040]** as shown below:

[040] The following embodiments are specifically contemplated herein.

Embodiment 1

A composition comprising dapsone, a first solubilizing agent which is diethylene glycol monoethyl ether, optionally at least one second solubilizing agent, a polymeric viscosity builder, and water, wherein the dapsone is present in the composition at a concentration of about 3% w/w to about 10% w/w.

Embodiment 2

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 10% w/w to about 40% w/w.

Embodiment 3

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 20% w/w to about 30% w/w.

Embodiment 4

The composition of embodiment 1, wherein the diethylene glycol monoethyl ether is present in the composition at a concentration of about 25% w/w.

Embodiment 5

The composition of embodiment 1, further comprising adapalene.

Embodiment 6

The composition of embodiment 5, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 7

The composition of embodiment 1 wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 8

The composition of embodiment 1, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 9

The composition of embodiment 8, wherein the second solubilizing agent is propylene glycol.

Embodiment 10

The composition of embodiment 9, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 11

The composition of embodiment 8, wherein the second solubilizing agent is propylene carbonate.

Embodiment 12

The composition of embodiment 11, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 13

The composition of embodiment 8, wherein the second solubilizing agent is ethanol.

Embodiment 14

The composition of embodiment 13, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 15

The composition of embodiment 1, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 16

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 17

The composition of embodiment 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 18

The composition of embodiment 1, further comprising methyl paraben.

Embodiment 19

The composition of embodiment 1, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 20

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 21

The composition of embodiment 19, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 22

The composition of embodiment 19, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 23

The composition of embodiment 19, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 24

The composition of embodiment 1, further comprising a neutralizing agent.

Embodiment 25

The composition of embodiment 24 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 26

The composition of embodiment 1 further comprising a chelating agent.

Embodiment 27

The composition of embodiment 26, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 28

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 29

The composition of embodiment 27, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 30

The composition of embodiment 1 wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 31

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1.

Embodiment 32

The method of embodiment 31 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis ~~piralis,~~ pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, ~~pruritis,~~ pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 33

The method of embodiment 32 wherein the condition is acne vulgaris.

Embodiment 34

The composition of embodiment 1, 2, 3, or 4, further comprising adapalene.

Embodiment 35

The composition of embodiment 34, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.

Embodiment 36

The composition of embodiment 1, 2, 3, 4, 34, or 35, wherein the second solubilizing agent is selected an alcohol, a glycol, an ester, or an ether.

Embodiment 37

The composition of embodiment 1, 2, 3, 4, 34, 35, or 36, wherein the second solubilizing agent is PEG 400, lactic acid, dimethyl isosorbide, propylene glycol, propylene carbonate, hexylene glycol, isostearyl alcohol, diethyl sebacate, or ethanol.

Embodiment 38

The composition of embodiment 37, wherein the second solubilizing agent is propylene glycol.

Embodiment 39

The composition of embodiment 38, wherein the propylene glycol is present in the composition at a concentration of about 5% w/w.

Embodiment 40

The composition of embodiment 37, wherein the second solubilizing agent is propylene carbonate.

Embodiment 41

The composition of embodiment 40, wherein the propylene carbonate is present in the composition at a concentration of about 5% w/w.

Embodiment 42

The composition of embodiment 37, wherein the second solubilizing agent is ethanol.

Embodiment 43

The composition of embodiment 42, wherein the ethanol is present in the composition at a concentration of about 3% w/w.

Embodiment 44

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.

Embodiment 45

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, or 44, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.

Embodiment 46

The composition of embodiment 45, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

Embodiment 47

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46, further comprising methyl paraben.

Embodiment 48

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

Embodiment 49

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.7% w/w to about 1.5% w/w.

Embodiment 50

The composition of embodiment 48, wherein the Carbomer Homopolymer Type C is present at a concentration of about 0.85% w/w to about 1.5% w/w.

Embodiment 51

The composition of embodiment 48, wherein the Carbomer interpolymer Type A is present at a concentration of about 1% w/w to 2% w/w.

Embodiment 52

The composition of embodiment 48, wherein the Carbomer interpolymer Type B is present at a concentration of about 0.1% w/w to about 0.5% w/w.

Embodiment 53

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, further comprising a neutralizing agent.

Embodiment 54

The composition of embodiment 53 wherein the neutralizing agent is NaOH or triethanolamine.

Embodiment 55

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, or 54, further comprising a chelating agent.

Embodiment 56

The composition of embodiment 55, wherein the chelating agent is ethylene diamine tetraacetic acid.

Embodiment 57

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present at a concentration of about 0.02% w/w to about 0.04% w/w.

Embodiment 58

The composition of embodiment 56, wherein the ethylene diamine tetraacetic acid is present in the composition at about 0.03% w/w.

Embodiment 59

The composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, or 58, wherein the composition is in the form of a gel, a suspension, an emulsion, a cream, a liquid, a paste, a lotion, a nanoemulsion, a microemulsion, a reverse emulsion, or a liposomal cream.

Embodiment 60

A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of embodiment 1, 2, 3, 4, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, or 59.

Embodiment 61

The method of embodiment 60 wherein the condition is acne vulgaris, rosacea, atopic dermatitis, treatment of chronic wounds, bed sores, keratosis ~~piralis,~~ pilaris, sebaceous cysts, inflammatory dermatoses, post inflammatory hyperpigmentation, eczema, xerosis, ~~pruritis,~~ pruritus, lichen planus, nodular prurigo, dermatitis, eczema, or miliaria.

Embodiment 62

The method of embodiment 60 wherein the condition is acne vulgaris.

Amendments to the Claims:

The following claims replace all claims previously submitted in this application. Only those claims being amended herein show their changes in highlighted form, where insertions appear as underlined text (e.g., insertions) while deletions appear as strikethrough or surrounded by double brackets (e.g. ~~deletions~~ or [[deletions]]).

1. (**Currently Amended**) A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

   about 7.5% w/w dapsone;

   about 30% w/w to about 40% w/w diethylene glycol monoethyl ether;

   about 2% w/w to about 6% w/w of a polymeric viscosity builder comprising ~~consisting of~~ acrylamide/sodium acryloyldimethyl taurate copolymer; and

   water;

   wherein the topical pharmaceutical composition does not comprise adapalene.

2. (Original) The method of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

3. (Original) The method of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

4. (Original) The method of claim 1, wherein the topical pharmaceutical composition further comprises methyl paraben.

5. – 6. (**Canceled**)

7. (**Currently Amended**) A method for treating a dermatological condition selected from the group consisting of acne vulgaris and rosacea comprising administering to a subject having the dermatological condition selected from the group consisting of acne vulgaris and rosacea a topical pharmaceutical composition comprising:

about 7.5% w/w dapsone;

about 30% w/w diethylene glycol monoethyl ether;

about 4% w/w of a polymeric viscosity builder comprising ~~consisting of~~ acrylamide/sodium acryloyldimethyl taurate copolymer; and

water;

wherein the topical pharmaceutical composition does not comprise adapalene.

8. (Original) The method of claim 7, wherein the topical pharmaceutical composition further comprises methyl paraben.

9. – 10. (Canceled).

11. (**Currently Amended**) The method of claim 1[[6]] wherein the dermatological condition is acne vulgaris.

12. (**Currently Amended**) The method of claim 7[[10]] wherein the dermatological condition is acne vulgaris.

REMARKS

This Reply responds to the Office Action sent March 7, 2016, in which the Office Action rejected Claims 1-5 and 7-9. Claims 1, 7, 11, and 12 have been amended. Claims 5-6 and 9-10 have been canceled. Thus Claims 1-4, 7-8, and 11-12 are currently pending. No new matter has been added by this amendment, and all amendments to the claims are fully supported by the originally filed specification and claims. The Applicants respectfully submit that the claims are in condition for allowance.

The Applicants note that Claims 1 and 7 have amended the element of "a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer" to a "polymeric viscosity builder **comprising** acrylamide/sodium acryloyldimethyl taurate copolymer." The Applicants submit that the pending Claims are still patentable in view of the cited prior art, and that relevant arguments made in the response and the declaration submitted on February 18, 2016 still support the patentability of the amended pending claims.

Allowable Subject Matter

The Applicants acknowledge the March 7, 2016 Office Action's observation that claims 6 and 10-12 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in dependent form. The Applicants have amended claim 1 to recite the elements of claim 6 and claim 7 to recite the elements of claim 10. Thus, the Applicants submit that the claims are allowable.

Claim Rejections

35 U.S.C. § 112(a)

Claims 1-5 and 7-9 were rejected under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, because the specification, while being enabling for administering the claimed topical dapsone preparation for the treatment of acne vulgaris or rosacea, does not reasonably provide enablement for administering the claimed topical dapsone preparation for the treatment of any other dermatological condition.

While the Applicants disagree with the rejection for at least the reasons cited in the February 18, 2016 response, solely in order to expedite prosecution, the claims have been amended. The Applicants submit that the amendments to the claims render the rejection under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph moot. Thus, the Applicants respectfully request that the claim rejections under 35 U.S.C § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph be withdrawn

Applicant requests a Notice of Allowance. The Examiner is invited to call the undersigned attorney if any issues remain unresolved.

Please use Deposit Account 01-0885 for the payment of any extension of time fees, and/or the payment of any other fees due in connection with the present response.

Dated: September 7, 2016

Respectfully submitted,

/Laura L. Wine/

Laura L. Wine
Reg. No. 68681
Attorney for Applicant

Please direct all inquiries and correspondence to:

Laura L. Wine
Allergan, Inc.
2525 Dupont Drive, T2-7H
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Tel: 714.246-4758/Fax: 714.246-6996

Electronic Patent Application Fee Transmittal

Application Number:	14885805
Filing Date:	16-Oct-2015
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	19107 DIV (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
RCE- 1st Request	1801	1	1200	1200
		Total in USD ($)		**2600**

Electronic Acknowledgement Receipt

EFS ID:	26858257
Application Number:	14885805
International Application Number:	
Confirmation Number:	9004
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	19107 DIV (AP)
Receipt Date:	07-SEP-2016
Filing Date:	16-OCT-2015
Time Stamp:	16:39:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2600
RAM confirmation Number	3558
Deposit Account	010885
Authorized User	Stein, Maria

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	19107DIV_RCE.pdf	1349874 afe2be260223f22fe168ed6c6d9b83333c3a50c3	no	3
Warnings:					
Information:					
2		19107DIV_Response_FOA_09072016.pdf	104856 c5bd0d6b2ec54957e5236b0d69cde88c76894e7e	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Response After Final Action	1	1
Specification	2	11
Claims	12	13
Applicant Arguments/Remarks Made in an Amendment	14	15

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32809 f53127e1ed99774a88e2b19dfa87e6aab0b30af4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1487539		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/885,805	Filing Date 10/16/2015	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **09/07/2016**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
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LIE
MARISSA BLYTHER

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51957 7590 09/30/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 09/30/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

TITLE OF INVENTION: TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/30/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 09/30/2016
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

TITLE OF INVENTION: TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/30/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
DRAPER, LESLIE A ROYDS	1629	514-646000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

51957 7590 09/30/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
DRAPER, LESLIE A ROYDS	

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 09/30/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/885,805	Applicant(s) WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the request for continued examination filed 07 September 2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-4,7,8,11 and 12*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☒ Other *Drawings filed 10/16/15 are accepted*.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 7, 2016 has been entered.

Claims 1-4, 7, 8, 11 and 12 remain pending and under examination. Claims 5, 6, 9 and 10 are cancelled. Claims 1, 7, 11 and 12 are amended.

EXAMINER'S COMMENTS

In reply to the rejection of claims 1-5 and 7-9 under the enablement provision of 35 U.S.C. §112(a) (pre-AIA first paragraph) as set forth at p.4-7 of the previous Office Action dated March 7, 2016, Applicant now presents newly amended independent claims 1 and 7 to be limited solely to the treatment of acne vulgaris or rosacea consistent with the embodiments determined to be adequately enabled by Applicant's as-filed specification. In view of these amendments to claims 1 and 7, and further in view of the cancellation of claims 5 and 9 directed to various other dermatological conditions, the rejection of claims 1-5 and 7-9 is now withdrawn.

As a result of Applicant's most recent claim amendments set forth in the claim listing provided with the request for continued examination as filed September 7, 2016, Applicant's limitation of the instant claims specifically to the treatment of acne vulgaris or rosacea additionally overcomes the objection to claims 6 and 10-12 as being otherwise allowable but for the fact that each was dependent from a rejected base claim. As such, the objection to claims 6 and 10-12 is now withdrawn as well.

Applicant's attention is directed to the explanation provided at p.2-4 of the previous Office Action dated March 7, 2016 as to why the instantly claimed method is nonobvious over the cited prior art of record in view of the Warner Declaration filed under 37 C.F.R. §1.132 on February 18, 2016. Such reasons are incorporated by reference herein, but are not repeated in the interest of brevity.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Claims 1-4, 7, 8, 11 and 12 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

September 23, 2016

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	**Art Unit**
	Leslie A. Royds Draper	1629

CPC								
Symbol							**Type**	**Version**
A61K		31	/	192			F	2013-01-01
A61K		9	/	0014			I	2013-01-01
A61K		31	/	136			I	2013-01-01
A61K		31	/	145			I	2013-01-01
A61K		47	/	32			I	2013-01-01
A61K		47	/	10			I	2013-01-01
A61K		47	/	14			I	2013-01-01
A61K		47	/	183			I	2013-01-01
A61K		47	/	34			I	2013-01-01
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CPC Combination Sets									
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	136	I	1	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	192	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	23 Sept 16	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	**Art Unit**
	Leslie A. Royds Draper	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	31 / 136 (2006.01.01)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	23 Sept 16	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	**Art Unit**
	Leslie A. Royds Draper	1629

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
2	2														
3	3														
4	4														
	5														
	6														
6	7														
7	8														
	9														
	10														
5	11														
8	12														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	23 Sept 16	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

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BIB DATA SHEET

CONFIRMATION NO. 9004

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/885,805	10/16/2015	514	1629	19107 DIV (AP)

APPLICANTS
Allergan, Inc., Irvine, CA;

INVENTORS
Kevin S. Warner, Anaheim, CA;
Ajay P. Parashar, Fairfax, VA;
Vijaya Swaminathan, San Francisco, CA;
Varsha Bhatt, San Francisco, CA;

**** CONTINUING DATA ***************************
This application is a DIV of 14/082,955 11/18/2013 PAT 9161926
which claims benefit of 61/728,403 11/20/2012
and claims benefit of 61/770,768 02/28/2013

Drawings filed 10/16/15 are accepted.

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/28/2015

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /Leslie A. Royds Draper/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	3	10	2

ADDRESS
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599
UNITED STATES

TITLE
TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

FILING FEE RECEIVED		
1600	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	10110	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:52
L2	28439	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:53
L3	270088	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:53
L4	29	1 and 2 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:53
L5	29	4 and (water aqueous (purified adj2 water))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:54
L6	0	5 not 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 13:59
L7	171	1 and 2 and (water aqueous (purified adj2 water)) and (methylparaben$2 (methyl adj2 paraben$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:00
L8	99	7 and (@pd<="20121120" @ad<="20121120")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:00
L9	4	8 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:00
L10	932	1 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:01
L11	29	10 and 2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:01
L12	0	11 not 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:01

L13	155	7 and (acne (acne adj2 vulgaris))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:02
L14	13	13 and 3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2016/09/23 14:02
L15	62	(warner-kevin$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:03
L16	21	(parashar-ajay$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:03
L17	7	(swaminathan-vijaya$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:03
L18	6	(bhatt-varsha$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:03
L19	4396	(allergan$).as. (allergan$).aanm. (allergan$).in.	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:03
L20	79	15 16 17 18	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:04
L21	7	20 and 1	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:04
L22	78	19 and 1	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:05
L23	7	22 and 3	US-PGPUB; USPAT; USOCR	OR	ON	2016/09/23 14:05

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L24	646	(dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))).clm.	US-PGPUB; USPAT	OR	ON	2016/09/23 14:08
L25	1791	("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)).clm.	US-PGPUB; USPAT	OR	ON	2016/09/23 14:08
L26	28134	((acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")).clm.	US-PGPUB; USPAT	OR	ON	2016/09/23 14:09
L27	4	24 and 25 and 26	US-PGPUB; USPAT	OR	ON	2016/09/23 14:09
L28	744	((A61K31/136).CPC.)	US-PGPUB; USPAT	OR	ON	2016/09/23 14:09
L29	31	28 and 24	US-PGPUB; USPAT	OR	ON	2016/09/23 14:10
L30	10409	((A61K9/0014).CPC.)	US-PGPUB; USPAT	OR	ON	2016/09/23 14:10
L31	4	29 and 25 and 26	US-PGPUB; USPAT	OR	ON	2016/09/23 14:10
L32	20	28 and 30	US-	OR	ON	2016/09/23

			PGPUB; USPAT			14:10
L33	11	32 and 24	US-PGPUB; USPAT	OR	ON	2016/09/23 14:10

9/23/2016 2:13:18 PM
C:\Users\lroyds\Documents\EAST\Workspaces\14885805.wsp

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=> d his full

     (FILE 'HOME' ENTERED AT 15:23:15 ON 23 SEP 2016)

     FILE 'REGISTRY' ENTERED AT 15:23:22 ON 23 SEP 2016
                E "DAPSONE"/CN
L1             1 SEA ABB=ON  PLU=ON  DAPSONE/CN
                D L1

     FILE 'HCAPLUS' ENTERED AT 15:24:05 ON 23 SEP 2016

     FILE 'REGISTRY' ENTERED AT 15:25:38 ON 23 SEP 2016
                SET SMARTSELECT ON
L2              SEL PLU=ON  L1 1- CHEM :      67 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 15:25:38 ON 23 SEP 2016
L3         19971 SEA ABB=ON  PLU=ON  L2
L4         20008 SEA ABB=ON  PLU=ON  L3 OR DAPSON? OR (DIAMINO(W)DIPHENYL(W)(SUL
                 FON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULPHONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULFONYL]ANILINE")
L5          4784 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W)GLYCOL(W)MONOETHYL?
                 (W)ETHER?) OR (ETHOXY(W)DIGLYCOL?) OR TRANSCUTOL?
L6        102884 SEA ABB=ON  PLU=ON  (ACRYLAMID?) OR (SODIUM(W)ACRYLOYL(W)DIMETH
                 YL(W)TAURAT?) OR (ACRYLAMID?(2A)SODIUM(2A)ACRYLOYL(2A)DIMETHYL(
                 2A)TAURAT?) OR SEPINEO? OR ("SEPINEO"(2A)"600")
L7             1 SEA ABB=ON  PLU=ON  L4 AND L5 AND L6
                D L7 1 IBIB ED ABS

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 15:28:10 ON 23 SEP 2016

     FILE 'REGISTRY' ENTERED AT 15:28:20 ON 23 SEP 2016
                SET SMARTSELECT ON
L8              SEL PLU=ON  L1 1- CHEM :      67 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 15:28:21 ON 23 SEP 2016
L9         60139 SEA ABB=ON  PLU=ON  L8
L10        60317 SEA ABB=ON  PLU=ON  L9 OR DAPSON? OR (DIAMINO(W) DIPHENYL(W)(SU
                 LFON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULPHONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULFONYL]ANILINE")
L11         1612 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
                 MONOETHYL?(W) ETHER?) OR (ETHOXY(W) DIGLYCOL?) OR TRANSCUTOL?
L12        49955 SEA ABB=ON  PLU=ON  (ACRYLAMID?) OR (SODIUM(W) ACRYLOYL(W)
                 DIMETHYL(W) TAURAT?) OR (ACRYLAMID?(2A) SODIUM(2A) ACRYLOYL(2A)
                  DIMETHYL(2A) TAURAT?) OR SEPINEO? OR ("SEPINEO"(2A)"600")
L13            0 SEA ABB=ON  PLU=ON  L10 AND L11 AND L12

     FILE 'USPAT2, USPATFULL' ENTERED AT 15:29:08 ON 23 SEP 2016

     FILE 'REGISTRY' ENTERED AT 15:29:15 ON 23 SEP 2016
                SET SMARTSELECT ON
L14             SEL PLU=ON  L1 1- CHEM :      67 TERMS
                SET SMARTSELECT OFF

     FILE 'USPAT2, USPATFULL' ENTERED AT 15:29:15 ON 23 SEP 2016
L15        46905 SEA ABB=ON  PLU=ON  L14
L16        47502 SEA ABB=ON  PLU=ON  L15 OR DAPSON? OR (DIAMINO(W) DIPHENYL(W)(S
                 ULFON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULPHONYL]ANILINE"
                  OR "4-[(4-AMINOBENZENE)SULFONYL]ANILINE")
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```
L17       22942 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
                MONOETHYL?(W) ETHER?) OR (ETHOXY(W) DIGLYCOL?) OR TRANSCUTOL?
L18         145 SEA ABB=ON  PLU=ON  (SODIUM(W) ACRYLOYL(W) DIMETHYL(W)
                TAURAT?) OR (ACRYLAMID?(2A) SODIUM(2A) ACRYLOYL(2A) DIMETHYL(2A
                ) TAURAT?) OR SEPINEO? OR ("SEPINEO"(2A)"600")
L19          10 SEA ABB=ON  PLU=ON  L16 AND L17 AND L18
L20          10 DUP REM L19 (0 DUPLICATES REMOVED)
                     ANSWER '1' FROM FILE USPAT2
                     ANSWERS '2-10' FROM FILE USPATFULL
                D L20 1-10 IBIB ABS

     FILE 'HOME' ENTERED AT 15:31:28 ON 23 SEP 2016
                SAVE TEMP ALL L14885805/L


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   22 SEP 2016  HIGHEST RN 1998197-38-8
     DICTIONARY FILE UPDATES:  22 SEP 2016  HIGHEST RN 1998197-38-8

     CAS Information Use Policies apply and are available at:

     http://www.cas.org/legal/infopolicy

     TSCA INFORMATION NOW CURRENT THROUGH APRIL 29, 2016

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
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     on property searching in REGISTRY, refer to:

     http://www.cas.org/training/stn/database-specific

     FILE HCAPLUS

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     FILE COVERS 1907 - 23 Sep 2016 VOL 165 ISS 15
     FILE LAST UPDATED: 22 Sep 2016 (20160922/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Dec 2015
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Dec 2015

     HCAplus includes complete International Patent Classification (IPC)
     reclassification data for the third quarter of 2016.
```

HCAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 23 Sep 2016 (20160923/UP). FILE COVERS 1946 TO DATE.

MEDLINE(R) is a registered trademark of the U.S. National Library of Medicine (NLM).

The 2016 MEDLINE reload was completed on January 23, 2016. The 2016 MeSH thesaurus is available as a source of terminology for your sear

This file contains CAS Registry Numbers for easy and accurate substance identification.

See HELP RANGE before carrying out any RANGE search.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 21 September 2016 (20160921/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926 through 1968. These records have been re-indexed to match current BIOSIS indexing.

FILE EMBASE
FILE COVERS: Embase-originated material 1947 to 22 Sep 2016 (20160922/ED)
Unique MEDLINE content 1948 to present
Emtree thesaurus last updated September 2016

This file contains CAS Registry Numbers for easy and accurate substance identification.

The content in Embase Alert (EMBAL) is strictly complementary to that in Embase (EMBASE). EMBAL contains, at any given time, approximately 100,000 novel records not yet available in Embase. Search both databases for the most timely and comprehensive results.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 22 Sep 2016 (20160922/PD)
FILE LAST UPDATED: 22 Sep 2016 (20160922/ED)
HIGHEST GRANTED PATENT NUMBER: US9451736
HIGHEST APPLICATION PUBLICATION NUMBER: US20160278253
CA INDEXING IS CURRENT THROUGH 18 Sep 2016 (20160918/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 22 Sep 2016 (20160922/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

USPAT2 includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2016.

USPAT2 now includes the comprehensive Cooperative Patent Classification
(CPC). See HELP CPC for details.

To ensure comprehensive retrieval of US patent information, including
US patent application information, search USPAT2 in combination with
USPATFULL.

SELECT PN, PNK, PATS, AP, APPS, PRN and PRAI now bears a charge in this
file. Please see HELP COST for pricing.

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 22 Sep 2016 (20160922/PD)
FILE LAST UPDATED: 22 Sep 2016 (20160922/ED)
HIGHEST GRANTED PATENT NUMBER: US9451736
HIGHEST APPLICATION PUBLICATION NUMBER: US20160278272
CA INDEXING IS CURRENT THROUGH 18 Sep 2016 (20160918/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 22 Sep 2016 (20160922/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2015

USPATFULL includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2016.

USPATFULL now includes the comprehensive Cooperative Patent Classification
(CPC). See HELP CPC for details.

To ensure comprehensive retrieval of US patent information, including
US patent application information, search USPATFULL in combination with
USPAT2.

SELECT PN, PNK, PATS, AP, APPS, PRN and PRAI now bears a charge in this
file. Please see HELP COST for pricing.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14885805	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search (PALM Database, eDAN, EAST)	11/11/15	LARD
EAST Search (See Attached Search History)	11/11/15	LARD
Updated Inventor Search (PALM Database, eDAN, EAST)	03/02/16	LARD
Updated EAST Search (See Attached Search History)	03/02/16	LARD
Review Searches in Parent US Application No.14/082,955	03/02/16	LARD
Updated Inventor Search (PALM Database, EAST, PE2E)	09/23/16	LARD
Updated EAST Search (See Attached Search History)	09/23/16	LARD
STN Search (See Attached Search History)	09/23/16	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	See Attached Text Search History in EAST	09/23/16	LARD

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	23 September 2016

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 09/30/2016
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Laura L. Wine	(Depositor's name)
/Laura L. Wine/	(Signature)
November 4, 2016	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	10/16/2015	Kevin S. Warner	19107 DIV (AP)	9004

TITLE OF INVENTION: TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/30/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
DRAPER, LESLIE A ROYDS	1629	514-646000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Laura L. Wine
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Allergan, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Irvine, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 010885 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Laura L. Wine/ Date November 4, 2016

Typed or printed name Laura L. Wine Registration No. 68681

Electronic Patent Application Fee Transmittal

Application Number:	14885805
Filing Date:	16-Oct-2015
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Filer:	Laura Lee Wine/Maria Stein
Attorney Docket Number:	19107 DIV (AP)

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	27421365
Application Number:	14885805
International Application Number:	
Confirmation Number:	9004
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Laura Lee Wine/Maria Stein
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	19107 DIV (AP)
Receipt Date:	04-NOV-2016
Filing Date:	16-OCT-2015
Time Stamp:	13:55:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$960
RAM confirmation Number	110716INTEFSW00010394010885
Deposit Account	010885
Authorized User	Maria Stein

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	19107DIV_PTOL-85.pdf	114133 1d5aafbdf8c93e56bff441c7a8c678f48ff04f23	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30473 5da6c627785f7ed63ebe049ac4fe78dbb909ca7a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	144606		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/885,805	12/13/2016	9517219	19107 DIV (AP)	9004

51957 7590 11/22/2016

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Kevin S. Warner, Anaheim, CA;
Allergan, Inc., Irvine, CA;
Ajay P. Parashar, Fairfax, VA;
Vijaya Swaminathan, San Francisco, CA;
Varsha Bhatt, San Francisco, CA;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/1/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
ALLERGAN, INC.	TARO PHARMACEUTICAL INDUSTRIES LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,517,219 B2	12/13/2016	Allergan, Inc.
2			
3			
4			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/28/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
ALLERGAN, INC.	TARO PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,517,219 B2	12/13/2016	Allergan, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

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