Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-13)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Kevin S. Warner	Nonprovisional Application Number (if known):	19107US (AP)
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Krishna Banerjee/	Date Nov. 18, 2013
Name (Print/Typed) Krishna Banerjee	Practitioner Registration Number 43,317

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

AMN1017

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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.

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 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, both 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 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.
2. The composition of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 20% w/w to about 30% w/w.
3. The composition of claim 1, wherein the diethylene glycol monoethyl ether is present in the composition at a concentration of about 25% w/w.
4. The composition of claim 1, further comprising adapalene.
5. The composition of claim 5, wherein the adapalene is present at a concentration of about 0.1% w/w to about 0.3% w/w.
6. The composition of claim 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.
7. The composition of claim 8, wherein the second solubilizing agent is propylene glycol.
8. The composition of claim 8, wherein the second solubilizing agent is propylene carbonate.
9. The composition of claim 8, wherein the second solubilizing agent is ethanol.
10. The composition of claim 1, wherein the polymeric viscosity builder comprises an acrylamide/sodium acryloyldimethyltaurate copolymer.
11. The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 2% w/w to about 6% w/w.
12. The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.
13. The composition of claim 1, further comprising methyl paraben.

14. The composition of claim 1, further comprising Carbomer interpolymer type A, Carbomer interpolymer type B, or Carbomer Homopolymer Type C.

15. The composition of claim 1, further comprising a neutralizing agent.

16. The composition of claim 24 wherein the neutralizing agent is NaOH or triethanolamine.

17. The composition of claim 1 further comprising ethylene diamine tetraacetic acid.

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

19. The method of claim 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.

20. The method of claim 32 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

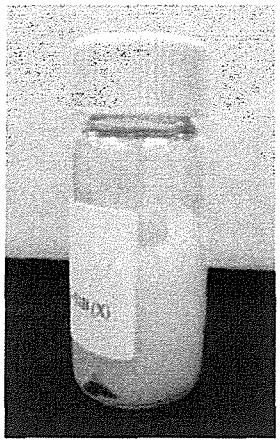
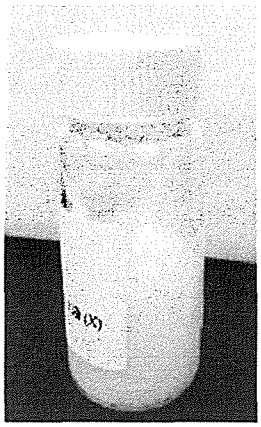
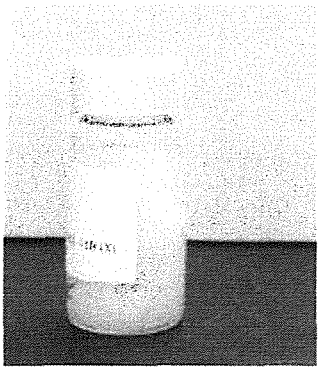
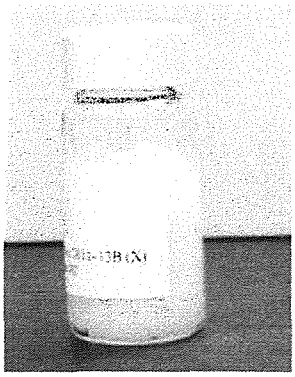
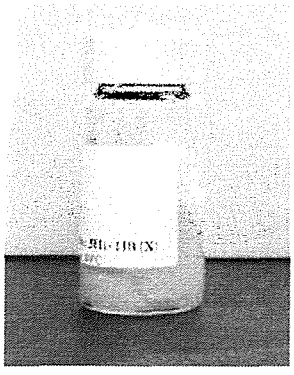
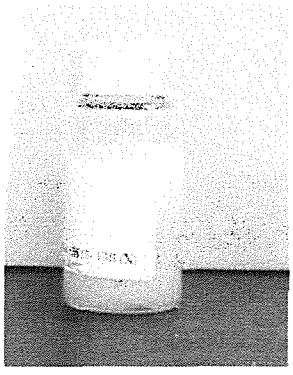
A1 at initial timepoint	**A2 at initial timepoint**
	
A1 after 4 weeks storage at 25^{0}C	**A2 after 4 weeks storage at 25^{0}C**
	
A1 after 4 weeks storage at 40^{0}C	**A2 after 4 weeks storage at 40^{0}C**
	

Figure 2. Polarized light images of dapsone in suspension formulations

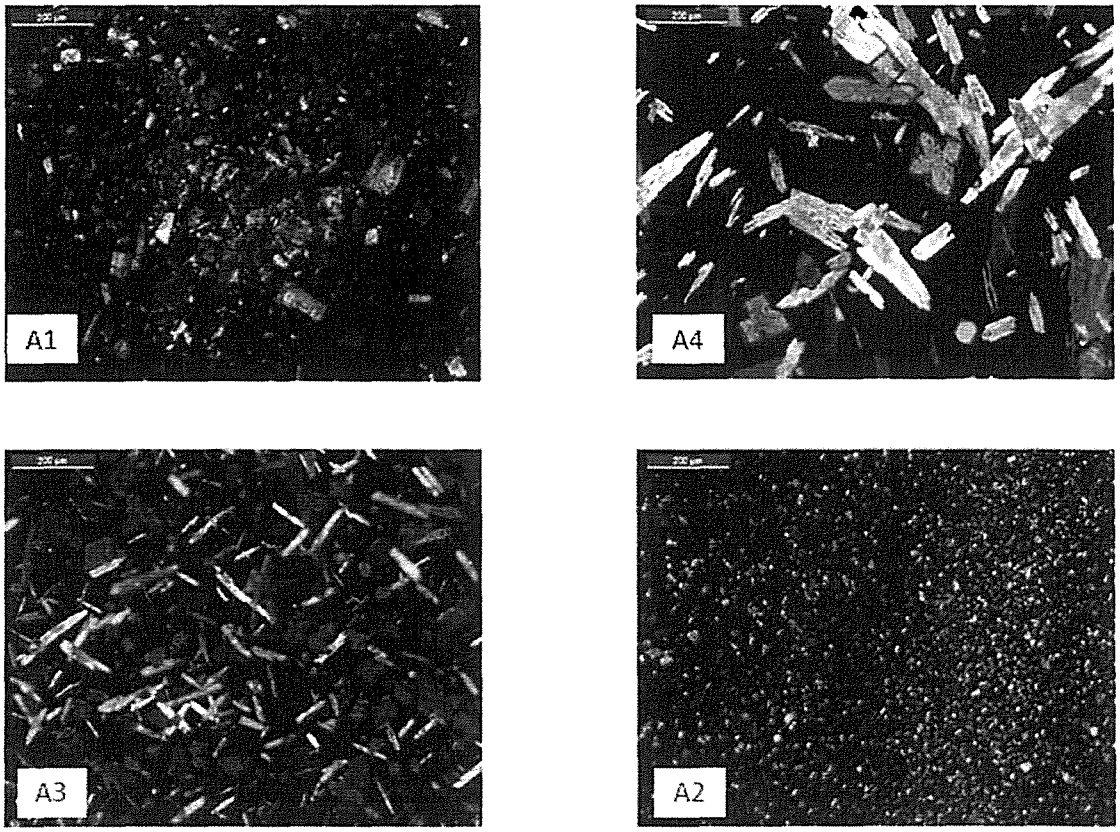
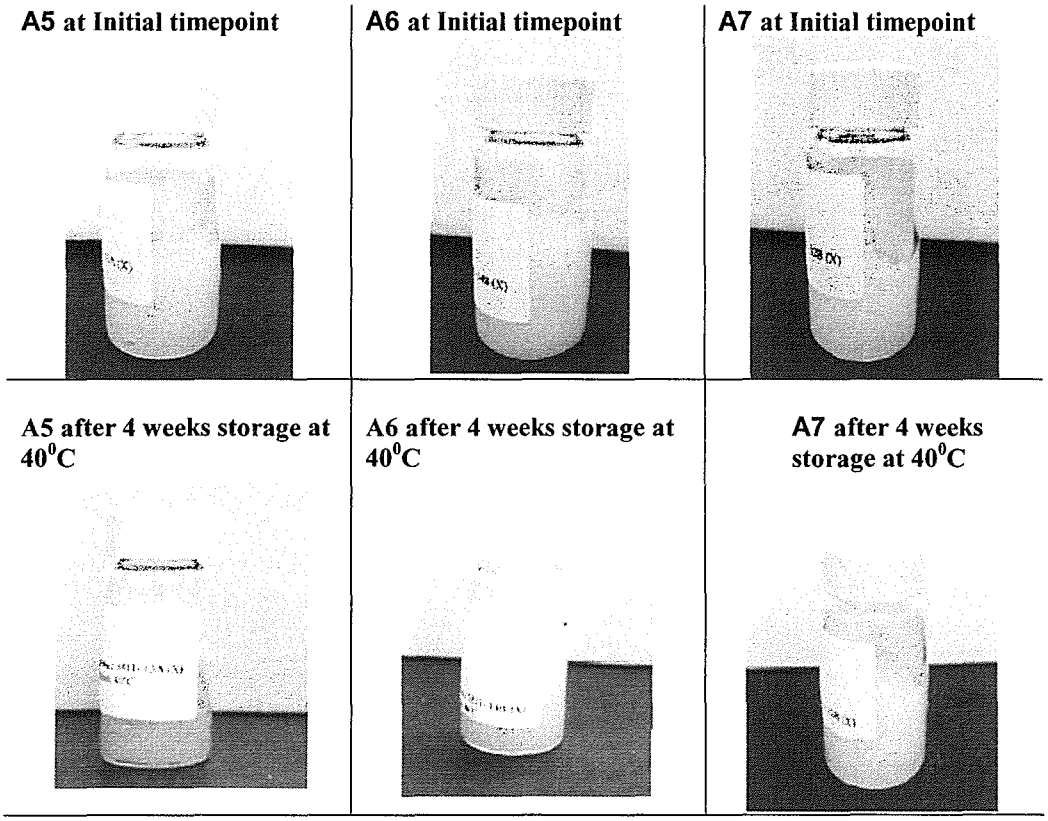


Figure 3. Appearance of formulations with antioxidants or chelating agents over 4 weeks



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Application Number	TBD
Filing Date	Herewith
First Named Inventor	Kevin S. Warner
Title	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	19107US (AP)

SIGNATURE of Applicant or Patent Practitioner

Signature	/Krishna Banerjee/	Date (Optional)	Nov. 18, 2013
Name	Krishna Banerjee	Registration Number	43,317
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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[ ] 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)

SIGNATURE of Applicant for Patent

Signature	/D Condino/	Date	09/20/2012
Name	Debra D. Condino, Reg. No. 31,007	Telephone	714-246-2388
Title and Company	Assistant Secretary, Allergan, Inc.		

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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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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.

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LEGAL NAME OF INVENTOR

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

Signature: _____

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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:

- [■] 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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

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

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.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

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

Signature: Kevin S. Warner

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.

PTO/AIA/14 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	19107US (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	San Diego	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	9085 Judicial Dr., Apt. 2530		
Address 2			
City	San Diego	State/Province	CA
Postal Code	92122	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	19107US (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	51957		
Email Address	patents_ip@allergan.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	19107US (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)	

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

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	51957		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(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.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61/728403	2012-11-20
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61/770768	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(d). 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(h)(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).

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

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Remove Access Code[i] (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

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 of 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.

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

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. [X]

Organization Name	Allergan, Inc.

Mailing Address Information:

Address 1	2525 Dupont Drive		
Address 2			
City	Irvine	**State/Province**	CA
Country [i]	US	Postal Code	92612
Phone Number	714-246-4249	Fax Number	714-246-5089
Email Address	patents_ip@allergan.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 is an Organization check here. [ ]

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

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

Mailing Address Information:

Address 1	
Address 2	

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

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

Remove

Signature:

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

Signature	/Krishna Banerjee/			Date (YYYY-MM-DD)	2013-11-18
First Name	Krishna	Last Name	Banerjee	Registration Number	43317

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

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 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.

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:	Krishna G. Banerjee/Rosemary Kaiwi
Attorney Docket Number:	19107US (AP)

Filed as Large Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

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
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**6030**

Electronic Acknowledgement Receipt

EFS ID:	17432763
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Krishna G. Banerjee/Rosemary Kaiwi
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	18-NOV-2013
Filing Date:	
Time Stamp:	16:52:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6030
RAM confirmation Number	4476
Deposit Account	010885
Authorized User	

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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	TrackOne Request	19107US_Req_for_Prioritized_Exam.pdf	45071 001db03729ae90ff386d6153a258801b64430638	no	2
Warnings:					
Information:					
2		19107US_Application_111813.pdf	210508 b471370fcc7e04d131047db7a2a45eb0ecd6cb2f	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	18
Claims	19	20
Abstract	21	21

Warnings:					
Information:					
3	Drawings-only black and white line drawings	19107US_Drawings_111813.pdf	3848051 af0c0a1812e959a43113ee3b989fe2dd0757f44a	no	3
Warnings:					
Information:					
4	Power of Attorney	19107US_Transmittal_POA.pdf	1853180 b63b24249f0fc3f4db3e79dbda58de272e5956ed	no	2
Warnings:					
Information:					
5	Oath or Declaration filed	19107US_Dec_Ajay.pdf	291219 6cb4fe48986a0f51e9bce2fc96f3a6b38b56f7fb	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	19107US_Dec_Varsha.pdf	672553 c5857c5fadbd2eba14d10210432bdd73fd48102	no	1
Warnings:					

Information:					
7	Oath or Declaration filed	19107US_Dec_Vijaya.pdf	2623863 f1dee66c22a65d39cb25c39b12168fd61e5e9b1d	no	1
Warnings:					
Information:					
8	Oath or Declaration filed	19107US_Dec_Warner.pdf	281012 9bc43a0657237467d4dc066eead79cd7a5579568	no	1
Warnings:					
Information:					
9	Application Data Sheet	19107US_ADS.pdf	1505202 9ce2346920cc1d8bac1770e1c97807020f9e66c1	no	7
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	40664 d22a585da12a0b2a0c70d9906a2ebb7115acbe52	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	11371323	

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.

Electronic Acknowledgement Receipt

EFS ID:	17432763
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Customer Number:	51957
Filer:	Krishna G. Banerjee/Rosemary Kaiwi
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	18-NOV-2013
Filing Date:	
Time Stamp:	16:52:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6030
RAM confirmation Number	4476
Deposit Account	010885
Authorized User	

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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	TrackOne Request	19107US_Req_for_Prioritized_Exam.pdf	45071 001db03729ae90ff386d6153a258801b64430638	no	2
Warnings:					
Information:					
2		19107US_Application_111813.pdf	210508 b471370fcc7e04d131047db7a2a45eb0ecd6cb2f	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	18
Claims	19	20
Abstract	21	21

Warnings:					
Information:					
3	Drawings-only black and white line drawings	19107US_Drawings_111813.pdf	3848051 af0c0a1812e959a43113ee3b989fe2dd0757f44a	no	3
Warnings:					
Information:					
4	Power of Attorney	19107US_Transmittal_POA.pdf	1853180 b63b24249f0fc3f4db3e79dbda58de272e5956ed	no	2
Warnings:					
Information:					
5	Oath or Declaration filed	19107US_Dec_Ajay.pdf	291219 6cb4fe48986a0f51e9bce2fc96f3a6b38b56f7fb	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	19107US_Dec_Varsha.pdf	672553 c5857c5fadbd2eba14d102101432bdd73fd48102	no	1
Warnings:					

Information:					
7	Oath or Declaration filed	19107US_Dec_Vijaya.pdf	2623863 f1dee66c22a65d39cb25c39b12168fd61e5e9b1d	no	1
Warnings:					
Information:					
8	Oath or Declaration filed	19107US_Dec_Warner.pdf	281012 9bc43a0657237467d4dc066eead79cd7a5579568	no	1
Warnings:					
Information:					
9	Application Data Sheet	19107US_ADS.pdf	1505202 9ce2346920cc1d8bac1770e1c97807020f9e66c1	no	7
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	40664 d22a585da12a0b2a0c70d9906a2ebb7115acbe52	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	11371323	

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/082,955	Filing Date 11/18/2013	☐ 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

	(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	

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
/MARY PEOPLES/

This collection of information is required by 37 CFR 1.16. 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/082,955	11/18/2013	1629	1900	19107US (AP)	20	1

CONFIRMATION NO. 1222

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

FILING RECEIPT

OC000000065317704

Date Mailed: 12/10/2013

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, San Diego, CA;
Vijaya Swaminathan, San Francisco, CA;
Varsha Bhatt, San Francisco, CA;

Applicant(s)

ALLERGAN, INC., IRVINE, CA

Assignment For Published Patent Application

ALLERGAN, INC., IRVINE, CA

Power of Attorney: The patent practitioners associated with Customer Number 51957

Domestic Priority data as claimed by applicant

This appln 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: 12/02/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/082,955**

Projected Publication Date: 05/22/2014

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: Yes

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.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/082,955

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
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))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 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) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)

CONFIRMATION NO. 1222

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

POA ACCEPTANCE LETTER

OC000000065313200

Date Mailed: 12/10/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/18/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/cbui/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313-1450
www.uspto.gov

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

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/082,955

1. THE REQUEST FILED November 18, 2013 IS **GRANTED.**

In view of the specific circumstances surrounding this application and, in particular, the filing of the Track 1 Request requirements, the Office hereby waives, *sua sponte*, the Processing Fee requirement of the Prioritized Examination, Track 1, program to the extent necessary to render the processing fee paid on the application filing date as sufficient to fulfill such requirement.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER, KEVIN S
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	19107-US-AP

U.S.PATENTS							Remove
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		
If you wish to add additional U.S. Patent citation information please click the Add button.							Add

U.S.PATENT APPLICATION PUBLICATIONS							Remove
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		
If you wish to add additional U.S. Published Application citation information please click the Add button.							Add

FOREIGN PATENT DOCUMENTS								Remove
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							☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER, KEVIN S
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	19107-US-AP

If you wish to add additional Foreign Patent Document citation information please click the Add button			Add
NON-PATENT LITERATURE DOCUMENTS			Remove
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		☐
If you wish to add additional non-patent literature document citation information please click the Add button			Add

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	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER, KEVIN S
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	19107-US-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.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

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	/Krishna Banerjee/	Date (YYYY-MM-DD)	2013-12-09
Name/Print	Krishna Banerjee	Registration Number	43,317

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.

Electronic Acknowledgement Receipt

EFS ID:	17661372
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Krishna G. Banerjee/Ken Dinh
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	13-DEC-2013
Filing Date:	18-NOV-2013
Time Stamp:	20:27:47
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	Information Disclosure Statement (IDS) Form (SB08)	19107-IDS_12_09_2013.pdf	595180 61e79d8493787205446576f64963221e19d6a055	no	4

Warnings:	
Information:	

Total Files Size (in bytes):	595180

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

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 01/22/2014

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
01/22/2014	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. 14/082,955	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 2 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 November 2013*.

☐ 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) *1-20* 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) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-20* 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: _____.

DETAILED ACTION

Claims 1-20 are presented for examination.

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

Requirement for Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-17, drawn to 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, classified in class 424, subclass 401.

II. Claims 18-20, drawn to a method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of 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, classified in class 514, subclass 709.

The inventions are distinct, each from the other, for the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the product as claimed can be used in materially different processes of using that product, such as, e.g., for treating acne vulgaris or for treating bed sores.

Restriction for examination purposes as indicated is proper because all of the inventions listed *supra* are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the

following reasons apply: (a) the inventions have acquired a separate status in the art in view of their different classification; (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; and (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, Applicant must indicate which of these claims are readable upon the elected invention.

Should Applicant traverse on the grounds that the inventions are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

ELECTION OF SPECIES REQUIREMENT

This application contains claims directed to patentably distinct species of (1) second solubilizing agent (claim 6); (2) carbomer polymer (claim 14); (3) neutralizing agent (claim 16); and (4) dermatological conditions (claim 19).

ELECTION OF INVENTION I REQUIRES APPLICANT TO MAKE THE FOLLOWING

SPECIES ELECTIONS:

(1) Election of a **single disclosed species** of second solubilizing agent from those specifically recited in instant claim 6, which are:

(i) PEG-400; (ii) lactic acid; (iii) dimethyl isosorbide; (iv) propylene glycol; (v) propylene carbonate; (vi) hexylene glycol; (vii) isostearyl alcohol; (viii) diethyl sebacate; or (ix) ethanol.

(2) Election of a **single disclosed species** of carbomer polymer from those specifically recited in instant claim 14, which are:

(x) carbomer interpolymer type A; (xi) carbomer interpolymer type B; or (xii) carbomer homopolymer type C.

(3) Election of a **single disclosed species** of neutralizing agent from those specifically recited in instant claim 16, which are:

(xiii) NaOH; or (xiv) triethanolamine.

ELECTION OF INVENTION II REQUIRES APPLICANT TO MAKE THE FOLLOWING SPECIES ELECTIONS:

(4) Election of a **single disclosed species** of optional second solubilizing agent from those specifically disclosed at p.7, para.[031], which are:

(xv) PEG-400; (xvi) lactic acid; (xvii) dimethyl isosorbide; (xviii) propylene glycol; (xix) propylene carbonate; (xx) hexylene glycol; (xxi) isostearyl alcohol; (xxii) diethyl sebacate; or (xxiii) ethanol.

(5) Election of a **single disclosed species** of dermatological condition to be treated from those specifically recited in instant claim 19, which are:

(xxiv) acne vulgaris; (xxv) rosacea; (xxvi) atopic dermatitis; (xxvii) chronic wounds; (xxviii) bed sores; (xxix) keratosis pilaris; (xxx) sebaceous cysts; (xxxi) post-inflammatory hyperpigmentation; (xxxii) eczema; (xxxiii) xerosis; (xxxiv) pruritis; (xxxv) lichen planus; (xxxvi) nodular prurigo; or (xxxvii) miliaria.

Note that the recited conditions of "inflammatory dermatoses" and "dermatitis" are generic at least to (xxvi) atopic dermatitis or (xxxii) eczema and, therefore, will be examined insofar as they read upon (xxvi) atopic dermatitis or (xxxii) eczema, if either (xxvi) atopic dermatitis or (xxxii) eczema is elected for examination.

Applicant is cautioned that the election of a particular species of compound(s) and/or condition, wherein the elected species is/are not adequately supported by the accompanying specification, may raise an issue of new matter under the written description requirement of 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph.

Currently, claims 1-6 and 10-20 are generic.

The species of additional agents (i.e., second solubilizing agents, carbomer polymers or neutralizing agents) to be used in combination with dapsone are independent or distinct because such agents recited in the claims are disparate in chemical structure and/or function such that a comprehensive search for one such agent or one such combination of agents would not necessarily result in a comprehensive search for any one or more other claimed agents or combinations thereof. As a result, a search and examination circumscribing all of the claimed species would be unduly burdensome because the species are not necessarily art-recognized equivalents and/or interchangeable in this regard. In addition, the consideration of the findings of such a search for compliance with the statutes and requirements set forth under 35 U.S.C. 101, 102, 103 and 112, would be additionally burdensome due to the disparate nature and significant breadth of agents (and, thus, combinations) encompassed by the instant claims. Furthermore, the combination of any one or more of such agents with the base composition of instant claim 1 would have imparted unique properties to the composition as a whole that are not necessarily equivalent to the properties observed with any one or more other combinations circumscribed by the claims.

The species of dermatological conditions are independent or distinct because the various conditions for which the claimed mixture of compounds must be therapeutically effective are each distinct from one another in etiology, pathophysiological manifestations, treatment protocol (i.e.,

duration of treatment, dosage amounts, frequency of treatment, etc.) and patient population such that a comprehensive search for the claimed mixture in an amount effective to treat, for example, acne vulgaris, would not necessarily anticipate, suggest or render obvious the administration of the same mixture in an amount effective to treat an etiologically and pathophysiologically distinct disorder, such as bed sores. In addition, the art does not necessarily recognize the entire genus of conditions encompassed by the claims as amenable to the same type of pharmacologic therapy.

Also, the claimed species are not necessarily obvious variants of each other based on the current record and there is a search and/or examination burden for these patentably distinct species as set forth above because at least the following reason(s) apply: (1) the species or groupings of patentably indistinct species have acquired a separate status in the art in view of their different classification and/or (2) the species or groupings of patentably indistinct species have acquired a separate status in the art due to their recognized divergent subject matter and/or (3) the species or groupings of patentably indistinct species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries).

Applicant is advised that a reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species,** including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 C.F.R. 1.144. If claims are added after the election, Applicant must indicate which of these claims

are readable on the elected species or grouping of patentably indistinct species.

Should Applicant traverse on the grounds that the species, or groups of patentably indistinct species from which election is required, are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, Applicant must indicate which are readable upon the elected species. MPEP §809.02(a).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The Examiner has required restriction between product or apparatus claims and process claims. Where Applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined

claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product/apparatus claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

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

January 14, 2014

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BIB DATA SHEET

CONFIRMATION NO. 1222

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/082,955	11/18/2013	514	1629	19107US (AP)

APPLICANTS

ALLERGAN, INC., IRVINE, CA, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

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

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

This appln claims benefit of 61/728,403 11/20/2012
and claims benefit of 61/770,768 02/28/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/02/2013

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	20	1

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		
1900	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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: : Kevin S. Warner et al.	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Draper, Leslie A Royds
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

RESPONSE TO RESTRICTION REQUIREMENT AND ELECTION OF SPECIES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

The following is in response to the Restriction Requirement in the Office Action mailed on January 22, 2014.

Remarks/Arguments begin on page 2 of this document.

REMARKS/ARGUMENTS

Election/Restriction

On pages 2-9 of the Action, the Examiner has restricted the claimed invention into two groups as set forth on page 2 of the Action. In response, **Applicants hereby elect the invention of Group I** without traverse.

Furthermore, as set forth on pages 4, the election of Invention I requires that Applicant makes the following species elections:

(1) Election of a single disclosed species of second solubilizing agent form those specifically recited in instant claim 6. **Applicant hereby elects propylene glycol as the second solubilizing agent.**

(2) Election of single disclosed species of carbomer polymer from those specifically recited in instant claim 14. **Applicant hereby elects carbomer homopolymer type C as the carbomer polymer.**

(3) Election of a single disclosed species of neutralizing agent from those specifically recited in instant claim 16. **Applicant hereby elects triethanolamine as the neutralizing agent.**

The claims encompassing the elected invention and species are claims 1-7 and 10-17.

The Commissioner is authorized to charge any fee which may be required in connection with this response to deposit account No. 01-0885.

Respectfully submitted,

Dated: February 20, 2014

/Krishna G. Banerjee/
Krishna G. Banerjee, Ph.D.
Registration No. 43,317
Attorney for Applicants

Please direct all inquiries and correspondenct to:
Krishna G. Banerjee, Ph.D.
Allergan, Inc. (T2-2H)
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714-246-5089/Facsimile: 714/246-4249

Electronic Acknowledgement Receipt

EFS ID:	18251787
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Krishna G. Banerjee/Rosemary Kaiwi
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	20-FEB-2014
Filing Date:	18-NOV-2013
Time Stamp:	13:16:35
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	Response to Election / Restriction Filed	19107US_Response_RR_022014.pdf	78212 be6b2858ecb8d22e45788355d8ebe3082425818a	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	78212

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New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 03/21/2014

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
03/21/2014	ELECTRONIC

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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. 14/082,955	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 *20 February 2014*.

☐ 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) *1-20* is/are pending in the application.

5a) Of the above claim(s) *8,9 and 18-20* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7 and 10-17* is/are rejected.

8)☐ Claim(s) _____ 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 *13Dec13*.

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 1-20 are presented for examination.

Acknowledgement is made of Applicant's claim for 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.

Applicant's Information Disclosure Statement (IDS) filed December 13, 2013 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08, the Examiner has considered the cited references.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group I (claims 1-17), directed to 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, and the election of (i) propylene glycol as the single disclosed species of second solubilizing agent; (ii) carbomer homopolymer type C as the single disclosed species of carbomer polymer; and (iii) triethanolamine as the single disclosed species of neutralizing agent, to which examination on the merits will be confined, in the reply filed February 20, 2014, is acknowledged by the Examiner.

Upon further reconsideration of the claims, the required election of a single disclosed species of neutralizing agent is hereby withdrawn.

Therefore, for the reasons above and those made of record at p.2-9 of the Office Action dated January 22, 2014, the requirement remains proper and is hereby made **FINAL**.

Claims 8-9 and 18-20 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

The claims that are drawn to the elected invention and elected species are claims 1-7 and 10-17 and such claims are herein acted on the merits.

Claim Rejections - 35 USC § 112(b)

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 1-5, 7 and 13-17 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.

In claim 1, the term "optionally" renders the claim indefinite because it is unclear if the term is intended to modify the "at least one second solubilizing agent" or if it is intended to modify the "at least one second solubilizing agent, a polymeric viscosity builder, and water". As a result, it is unclear which components are, in fact, optional. Clarification is required.

In claim 5, Applicant recites the "composition of claim 5", which renders the claim indefinite because it is unclear how claim 5 can depend from itself. Clarification is required. For the purposes of examination, claim 5 will be interpreted to depend from claim 4.

In claim 7, Applicant recites the "composition of claim 8, wherein the second solubilizing agent is propylene glycol", which renders the claim indefinite because claim 8 is directed to the second solubilizing agent as "propylene carbonate". It is unclear if Applicant intends to define the second solubilizing agent as propylene glycol *per se* (in which case the claim is further indefinite for failing to further limit instant claim 8) or whether Applicant intends to claim the use of two second solubilizing agents (i.e., "at least one" as provided for in instant claim 1) as part of the composition. Clarification is required.

In claim 16, Applicant recites the "composition of claim 24", which renders the claim indefinite because there is no claim 24 provided in the claim listing. Thus, it is unclear how claim 16 can depend

from a claim that has never been presented. Clarification is required. For the purposes of examination, claim 16 will be interpreted to depend from claim 15.

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

Claim Rejections - 35 USC § 102

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 the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claims 1-3, 6-7 and 13-16 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Lathrop et al. (U.S. Patent Application Publication No. 2006/0204526; 2006), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) to show a fact.

Lathrop et al. teaches topical emulsive compositions of dapsone (abstract). Lathrop et al. teaches the following exemplary compositions:

(i) Ex.1 (p.7, para.[0086]), which comprises 5% w/w dapsone; 25% w/w ethoxydiglycol (i.e., diethylene glycol monoethyl ether; see, e.g., p.5, para.[0056]); 0.2% w/w methylparaben; and purified water;

(ii) Ex.2 (p.7, para.[0093]), which comprises 3% w/w dapsone; 0.25% w/w CARBOPOL 980; 15% w/w ethoxydiglycol; 0.2% w/w methylparaben; 0.25% w/w sodium hydroxide solution; and purified water; and

(iii) Ex.8 (p.9, para.[0134]), which comprises 3% w/w dapsone; 15% w/w propylene glycol; 15% w/w ethoxydiglycol; 0.4% w/w CARBOPOL 980; 0.15% w/w methylparaben; triethanolamine; and purified water.

Lubrizol teaches that CARBOPOL 980 is a polymeric thickener synonymous with "carbomer homopolymer type C" as recited in Applicant's instant claim 14 (Table 1B; p.2).

Claims 1-7 and 11-17 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Ahluwalia et al. (WO 2011/014627; February 2011), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) and Garrett (WO 2009/108147 A1; 2009) to show facts.

Ahluwalia et al. teaches topical compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (abstract). Ahluwalia et al. teaches that dapsone/adapalene compositions preferably contain 0.5-10% w/w dapsone and 0.1-0.3% w/w adapalene (Table 1, p.8). Ahluwalia et al. teaches the following exemplary compositions:

(i) Table 2A teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 10% w/w or 20% w/w propylene glycol; 0.01% w/w EDTA; 0.75% w/w CARBOPOL 980; sodium hydroxide; and purified water;

(ii) Table 2B teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 15% w/w propylene glycol; 0.01% w/w EDTA; 2% w/w hydroxyethyl cellulose (i.e., a polymeric thickener, which meets Applicant's requirement directed to a "polymeric viscosity builder" as recited in instant claims 1 and 11-12); sodium hydroxide; and purified water; and

(iii) Fig.5 (Compositions 1 and 2) teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w TRANSCUTOL; 0.01% w/w EDTA disodium; 4% w/w hydroxyethyl cellulose (i.e., a polymeric thickener, which meets Applicant's requirement directed to a "polymeric viscosity builder" as recited in instant claims 1 and 11-12); sodium hydroxide; and water.

Lubrizol teaches that CARBOPOL 980 is a polymeric thickener synonymous with "carbomer homopolymer type C" as recited in Applicant's instant claim 14 (Table 1B; p.2).

Garrett teaches that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether as recited in Applicant's instant claims 1-3 (p.14, l.5-6).

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 1-7 and 10-17 are rejected under 35 U.S.C. 103 as being unpatentable over Ahluwalia et al. (WO 2011/014627 A1; February 2011), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) and Garrett (WO 2009/108147 A1; 2009) to show facts, in view of Hani et al. (WO 2010/105052 A1; 2010).

Ahluwalia et al. teaches topical compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (abstract). Ahluwalia et al. teaches that dapsone/adapalene compositions preferably contain, *inter alia*, 0.5-10% w/w dapsone and 0.1-0.3% w/w

adapalene, as well as 1-50% w/w diethylene glycol monoethyl ether and 1-8% w/w hydroxyethyl cellulose as a thickener (Table 1, p.8). Ahluwalia et al. teaches the following exemplary compositions:

(i) Table 2A teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 10% w/w or 20% w/w propylene glycol; 0.01% w/w EDTA; 0.75% w/w CARBOPOL 980; sodium hydroxide; and purified water;

(ii) Table 2B teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 15% w/w propylene glycol; 0.01% w/w EDTA; 2% w/w hydroxyethyl cellulose (i.e., a polymeric thickener, which meets Applicant's requirement directed to a "polymeric viscosity builder" as recited in instant claims 1 and 11-12); sodium hydroxide; and purified water; and

(iii) Fig.5 (Compositions 1 and 2) teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w TRANSCUTOL; 0.01% w/w EDTA disodium; 4% w/w hydroxyethyl cellulose (i.e., a polymeric thickener, which meets Applicant's requirement directed to a "polymeric viscosity builder" as recited in instant claims 1 and 11-12); sodium hydroxide; and water.

Lubrizol teaches that CARBOPOL 980 is a polymeric thickener synonymous with "carbomer homopolymer type C" as recited in Applicant's instant claim 14 (Table 1B; p.2).

Garrett teaches that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether as recited in Applicant's instant claims 1-3 (p.14, l.5-6).

Ahluwalia et al. does not expressly teach (1) the claimed range of dapsone (i.e., "about 3% w/w to about 10% w/w"; claim 1), the claimed range of diethylene glycol monoethyl ether (i.e., "about 20% w/w to about 30% w/w"; claim 2) or the claimed range of polymeric viscosity builder (i.e., hydroxyethyl cellulose; "about 2% w/w to about 6% w/w"; claim 11) or (2) the use of acrylamide/sodium acryloyldimethyltaurate copolymer as the polymeric viscosity builder (claim 10).

The teachings in Ahluwalia et al. provide for ranges of dapsone, diethylene glycol monoethyl ether and hydroxyethyl cellulose (i.e., a "polymeric viscosity builder" as claimed) that clearly circumscribe the ranges instantly claimed. See, e.g., Ahluwalia et al. at p.8, Table 1, which discloses the use of 0.5-10% w/w dapsone and 0.1-0.3% w/w adapalene, as well as 1-50% w/w diethylene glycol monoethyl ether

and 1-8% w/w hydroxyethyl cellulose as a thickener. Such ranges clearly encompass Applicant's instantly claimed ranges of:

(i) "about 3% w/w to about 10% w/w" dapsone (claim 1);

(ii) "about 20% w/w to about 30% w/w" diethylene glycol monoethyl ether (claim 2); or

(iii) "about 2% w/w to about 6% w/w" hydroxyethyl cellulose (claim 11).

Thus, Ahluwalia et al. clearly 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 Ahluwalia et al. within the disclosed ranges therein. This is because Ahluwalia et al. 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 Ahluwalia et al. 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.

Hani et al. teaches that acrylamide/sodium acryloyldimethyltaurate 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 hydroxyethyl cellulose thickener of the dapsone/adapalene formulations described in Ahluwalia et al. with acrylamide/sodium acryloyldimethyltaurate copolymer because each was well known in the art to be a suitable thickening agent for topical personal care products, as evidenced by Ahluwalia et al. 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 hydroxyethyl cellulose and acrylamide/sodium acryloyldimethyltaurate copolymer are 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").

Conclusion

Rejection of claims 1-7 and 10-17 is proper.

Claims 8-9 and 18-20 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

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 (MPEP §714.02 and §2163.06). Note that support should be provided for amendments to previously pending claims, as well as any newly added claims. In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, not the published application. Due to the procedure outlined in MPEP §2163.06 for interpreting claims, it is noted that 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.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A

copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

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 18, 2014

Notice of References Cited	Application/Control No. 14/082,955	Applicant(s)/Patent Under Reexamination WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 2009/108147 A1	09-2009	WO	Garrett	-
	O	WO 2010/105052 A1	09-2010	WO	Hani et al.	-
	P	WO 2011/014627 A1	02-2011	WO	Ahluwalia et al.	-
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	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>.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 September 2010 (16.09.2010)

PCT

(10) International Publication Number
WO 2010/105052 A1

(51) International Patent Classification:
A61K 8/02 (2006.01)

(21) International Application Number:
PCT/US2010/026976

(22) International Filing Date:
11 March 2010 (11.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/159,284 11 March 2009 (11.03.2009) US
61/170,278 17 April 2009 (17.04.2009) US

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(74) Agent: **DAVIS, William, J.**; International Specialty Products, 1361 Alps Road, Wayne, NJ 07470 (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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (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: TOPICAL PERSONAL CARE AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

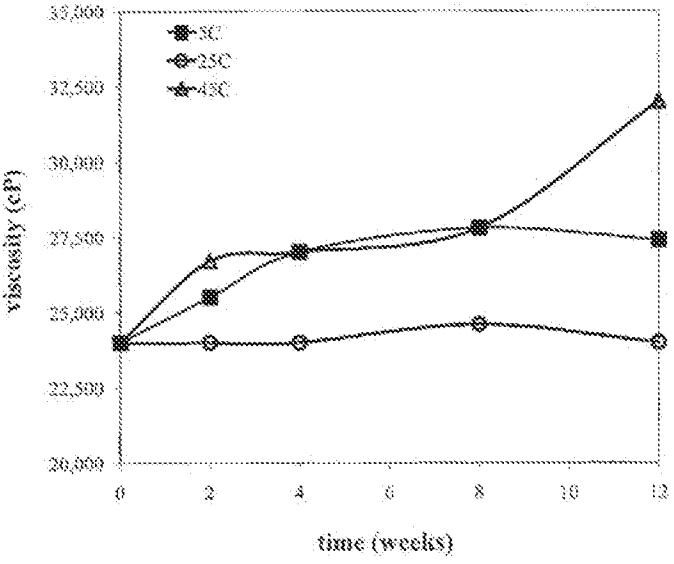

Fig. 1

(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.

[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)

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; digiycol/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; naito 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 crospolymer; sodium acrylate/sodium acrylamidomethylpropane sulfonate copolymer; sodium acrylates/vinyl isodecanoate crospolymer; 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.

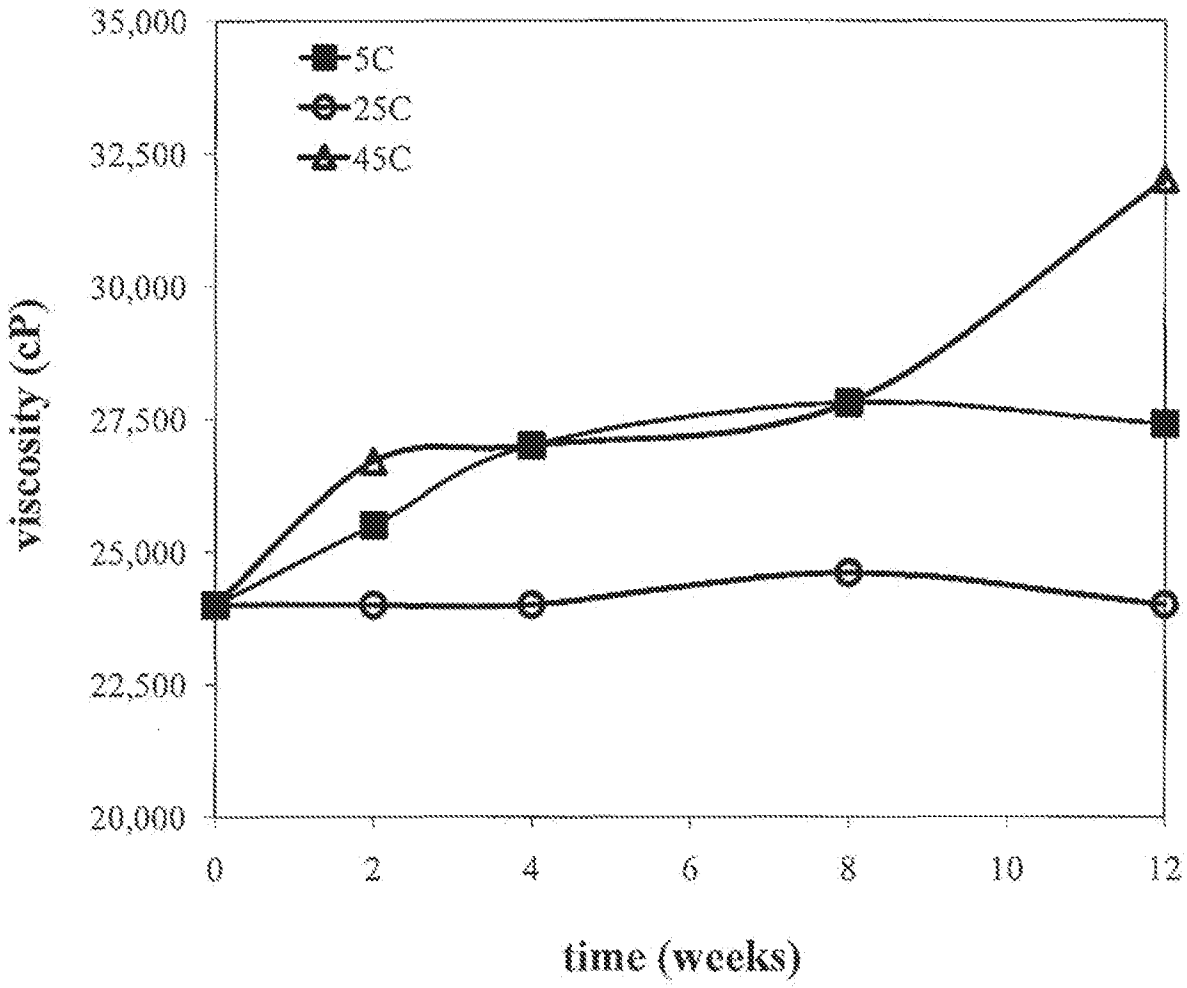
35,000
32,500
30,000
27,500
25,000
22,500
20,000
viscosity (cP)
5C
25C
45C
0
2
4
6
8
10
12
time (weeks)

Fig: 1

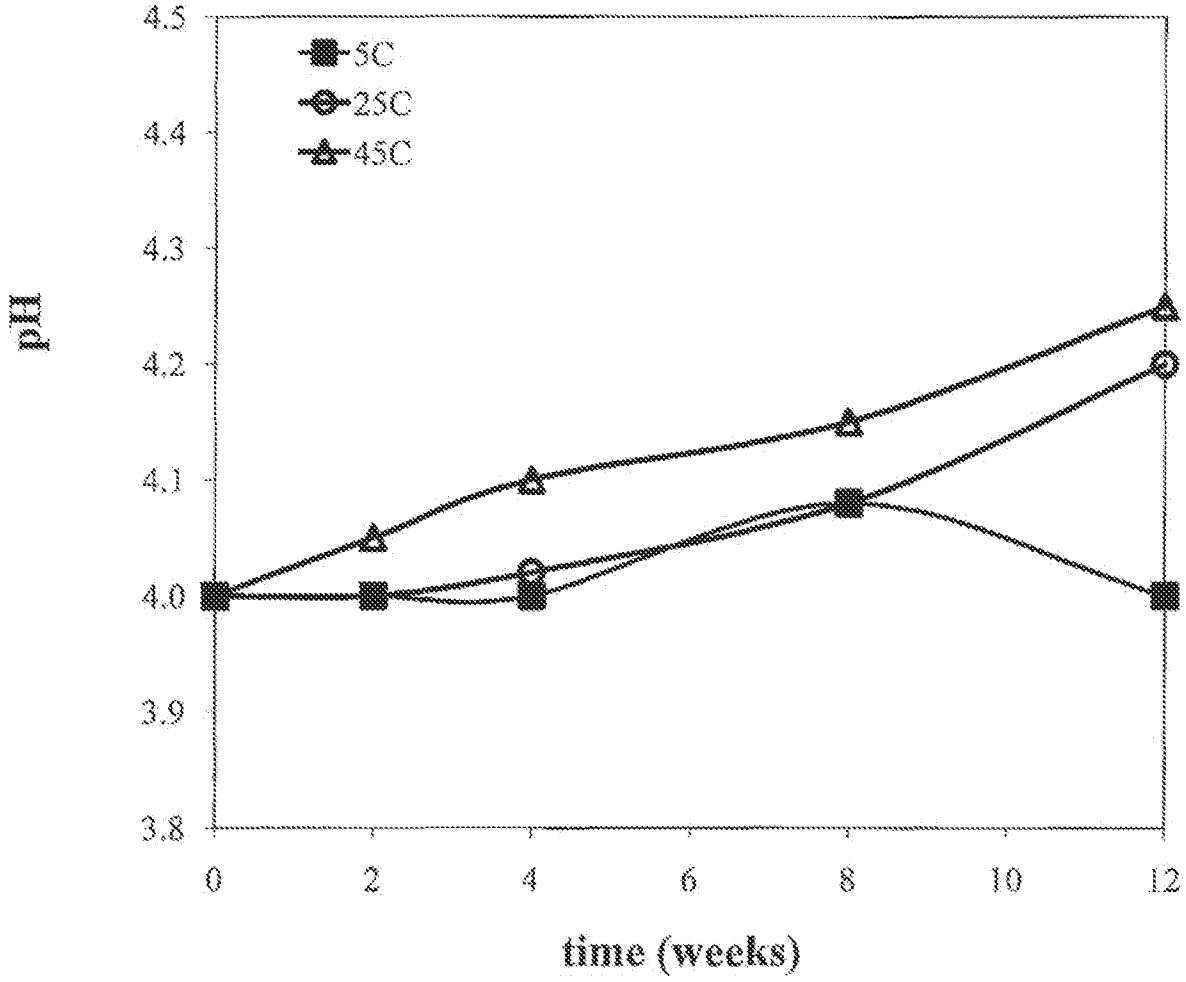

Fig. 2

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 - 424/401,409,59,65,66,68 (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 38-45; 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 (Braudigam et al.) 25 November 2004 (25.11.2004), entire disclosure, esp. para [0046]	20

☐ 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 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

Form PCT/ISA/210 (second sheet) (July 2009)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2009 (03.09.2009)

PCT

(10) International Publication Number
WO 2009/108147 A1

(51) International Patent Classification:
A61K 8/02 (2006.01)

(21) International Application Number:
PCT/US2008/002549

(22) International Filing Date:
27 February 2008 (27.02.2008)

(25) Filing Language: English

(26) Publication Language: English

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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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, 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: 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.

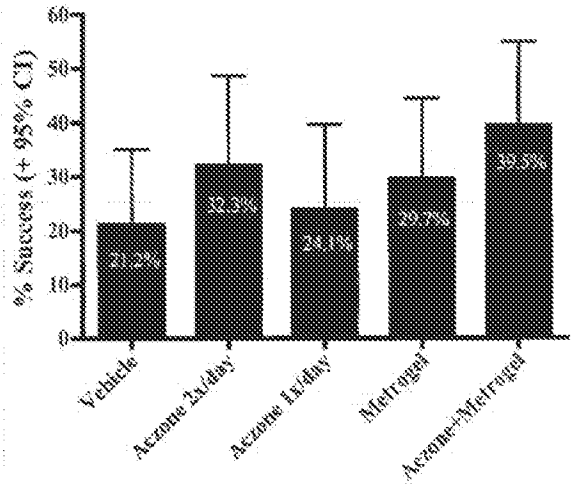

FIG. 11

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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 Assesement (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

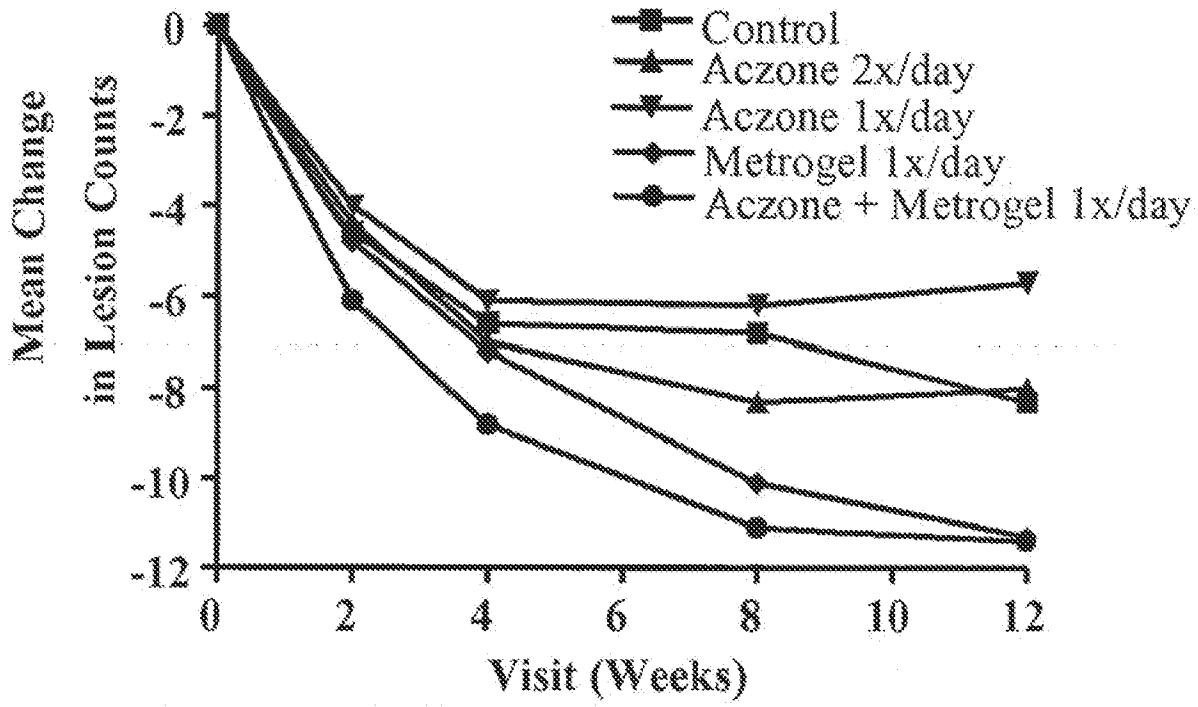
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
0
2
4
6
8
10
12
Visit (Weeks)
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day

FIG. 1

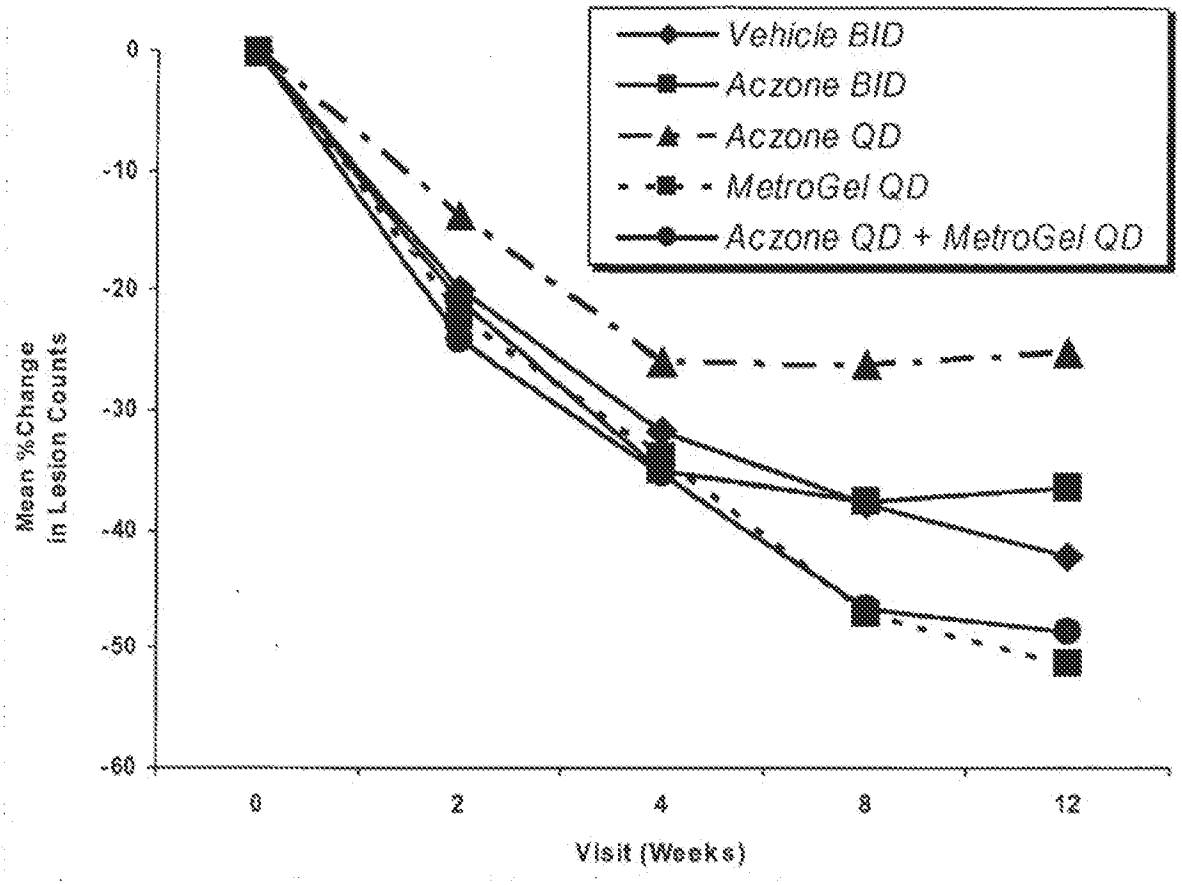
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 2

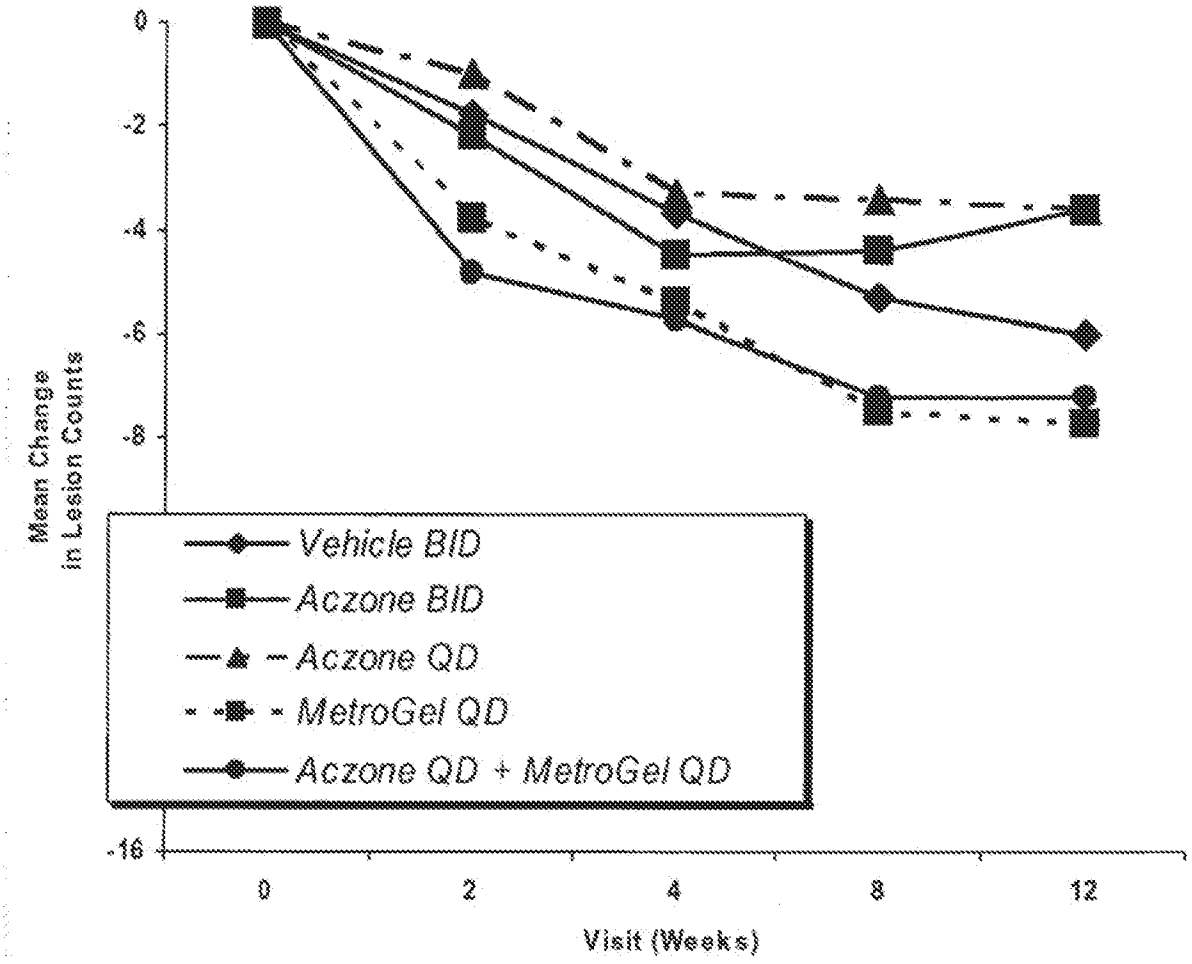
0
-2
-4
-6
-8
-16
Mean Change in Lesion Counts
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
0
2
4
8
12
Visit (Weeks)

FIG. 3

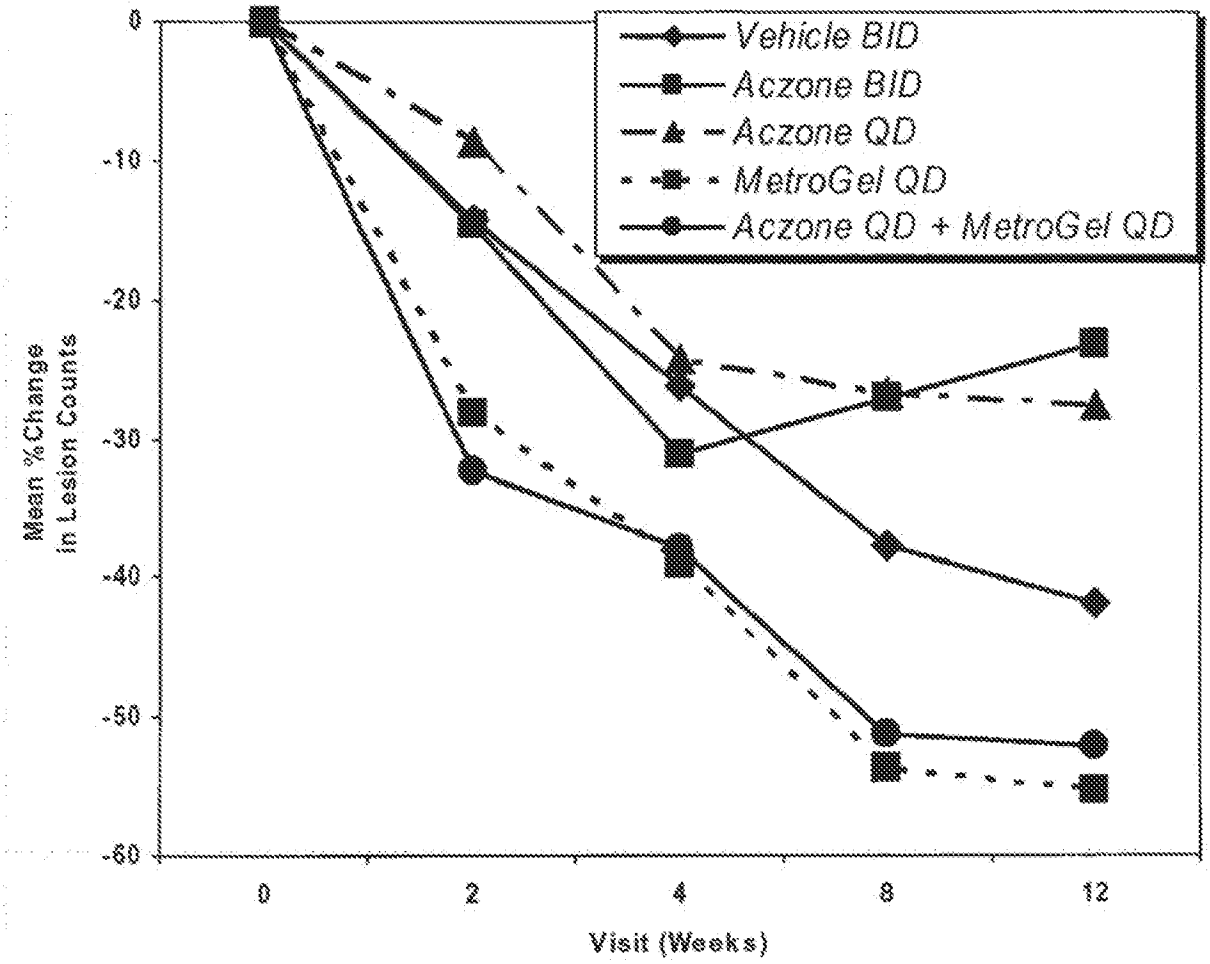
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 4

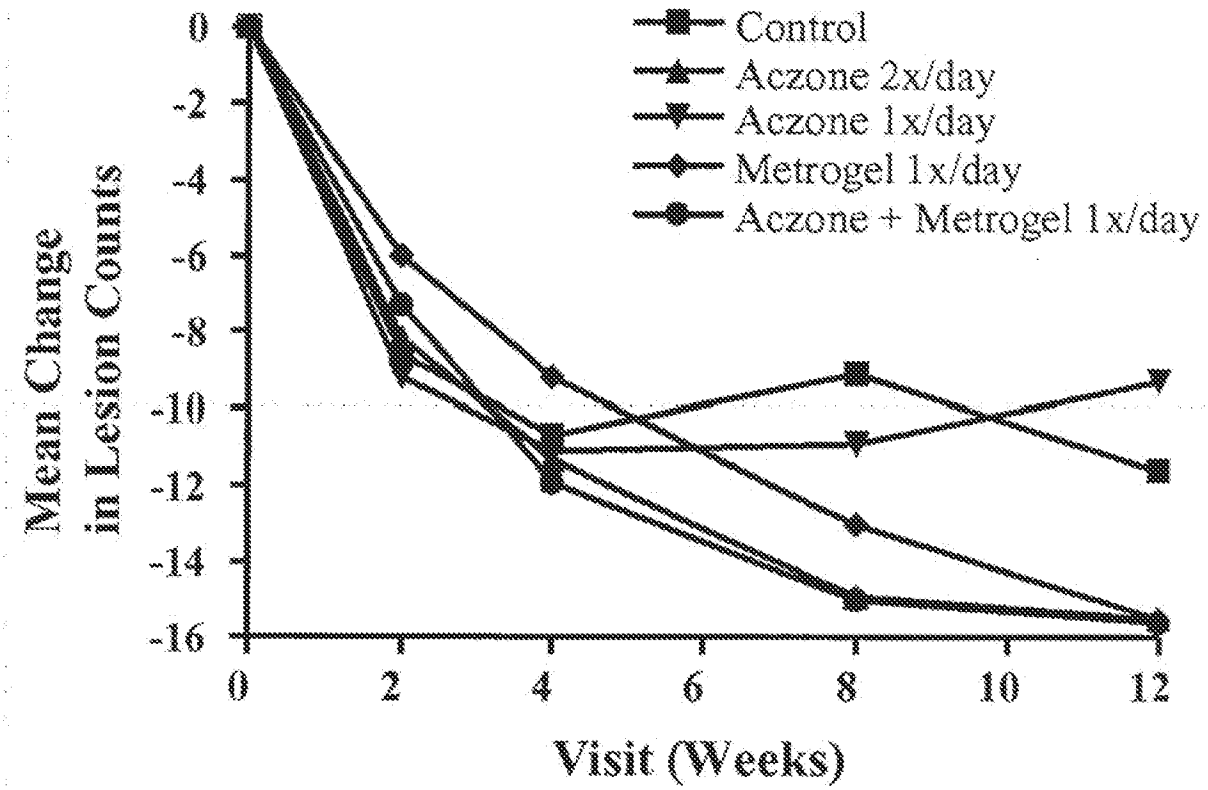
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
-14
-16
0
2
4
6
8
10
12
Visit (Weeks)

FIG. 5

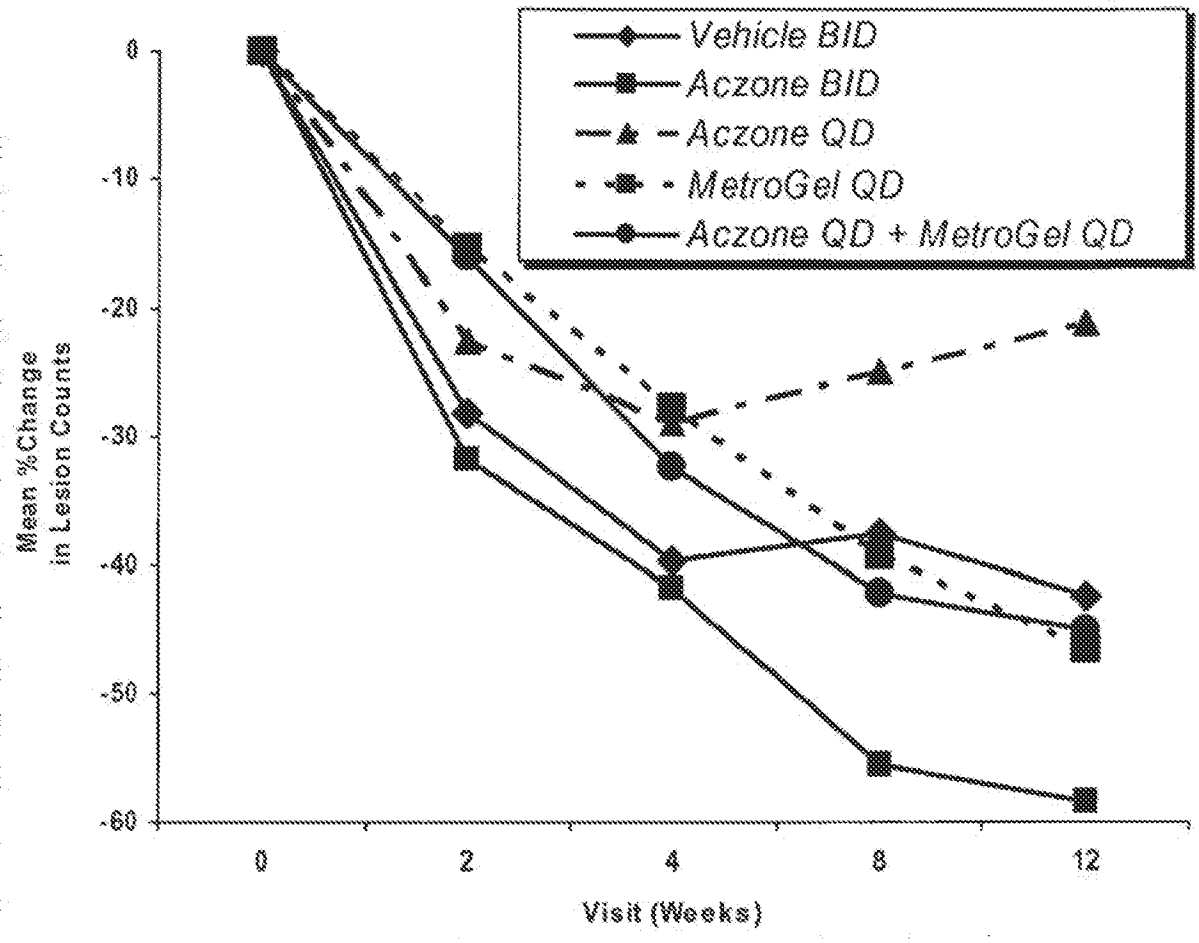
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean %Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 6

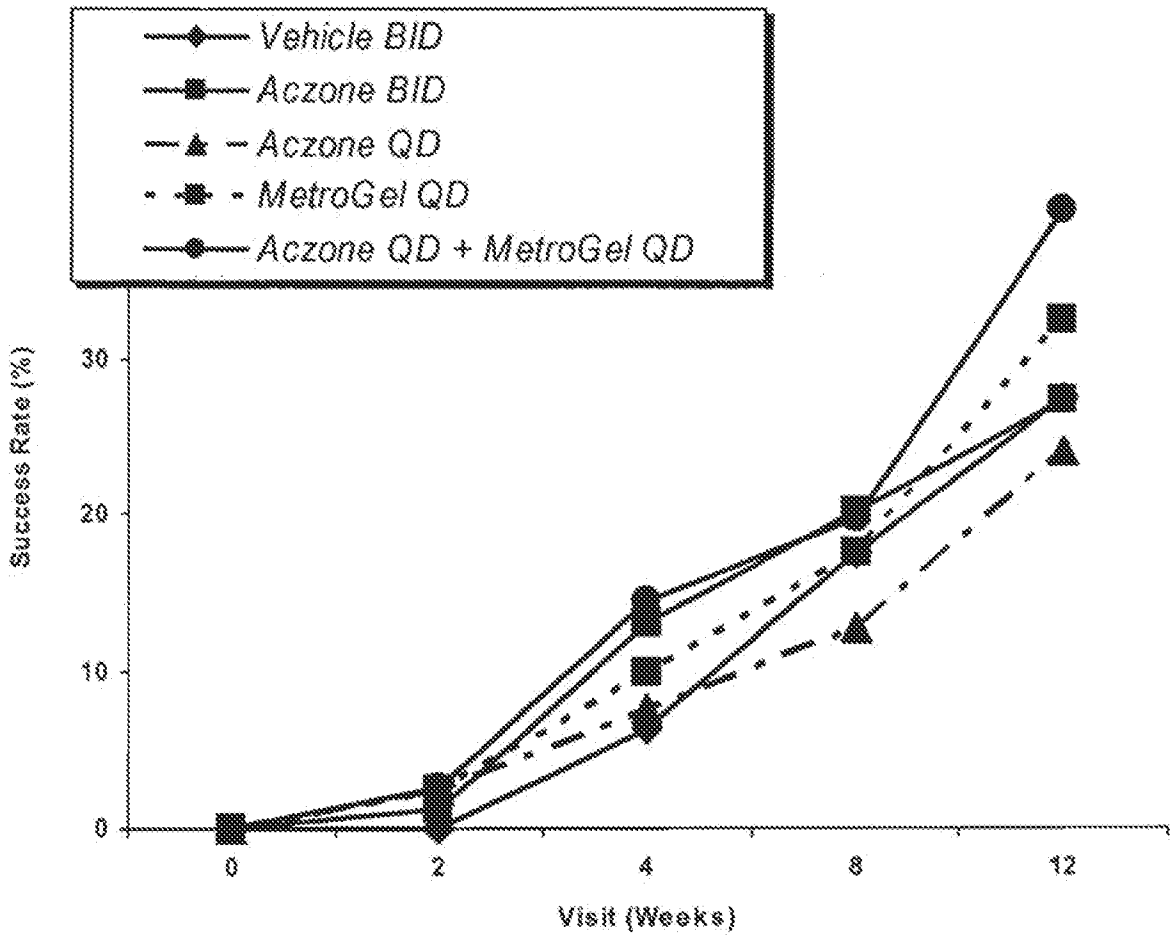
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Success Rate (%)
0
10
20
30
0
2
4
8
12
Visit (Weeks)

FIG. 7

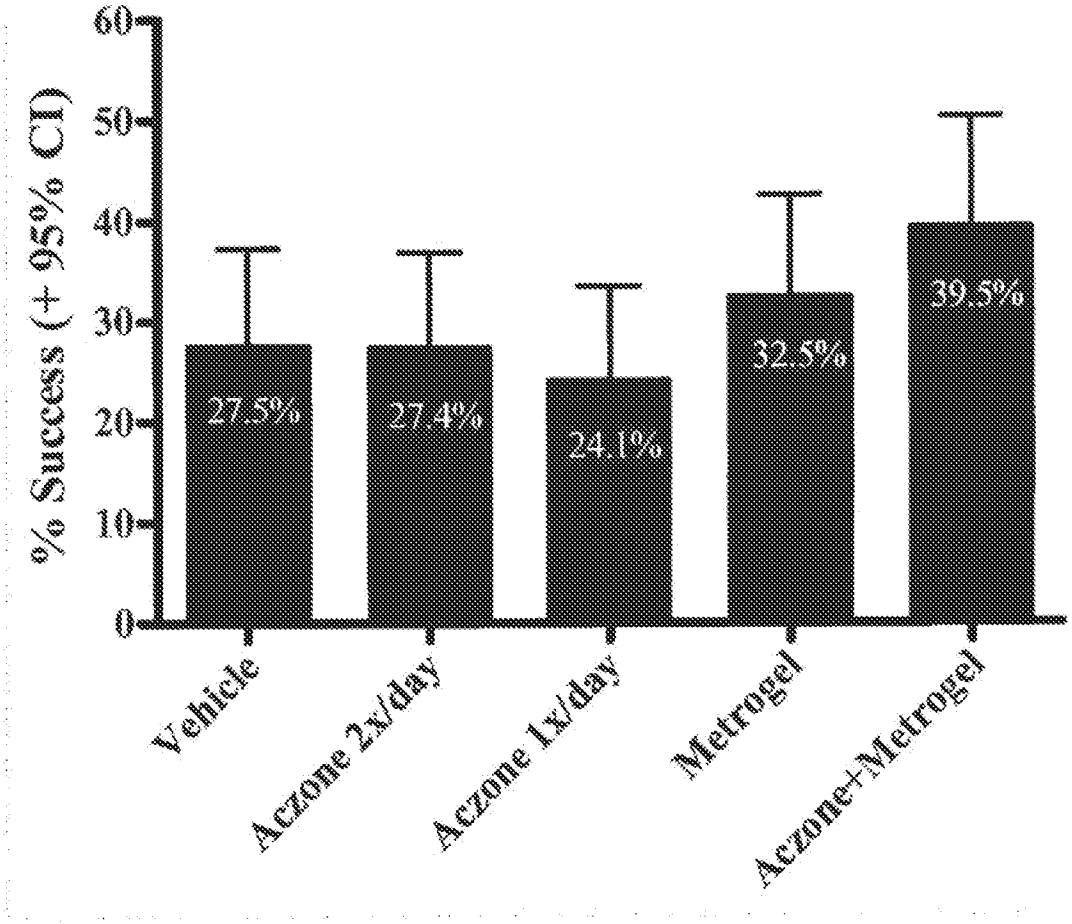
% Success (+ 95% CI)
60
50
40
30
20
10
0
27.5%
27.4%
24.1%
32.5%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

FIG. 8

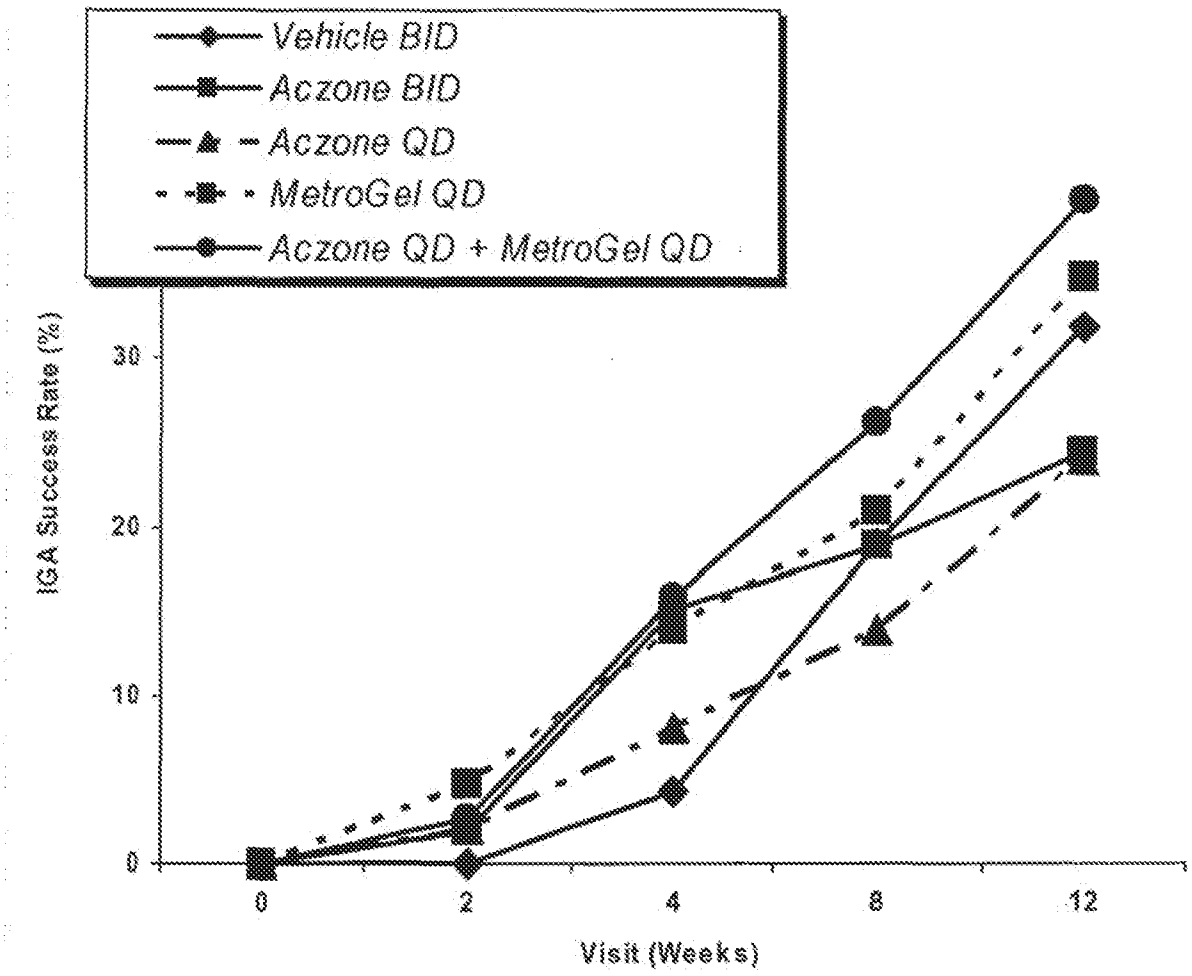
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
30
20
10
0
0
2
4
8
12
Visit (Weeks)

FIG. 9

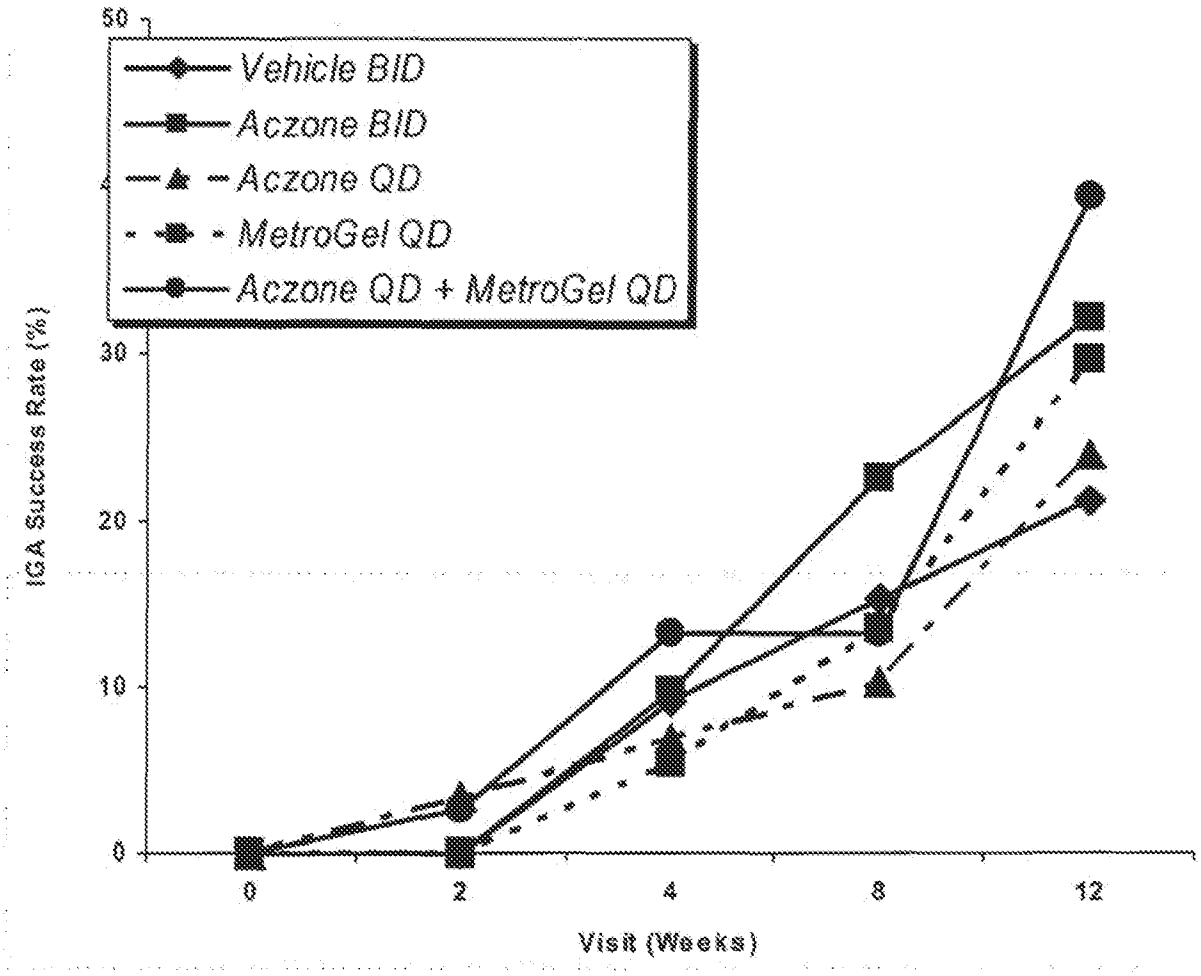
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
50
30
20
10
0
0
2
4
8
12
Visit (Weeks)

FIG. 10

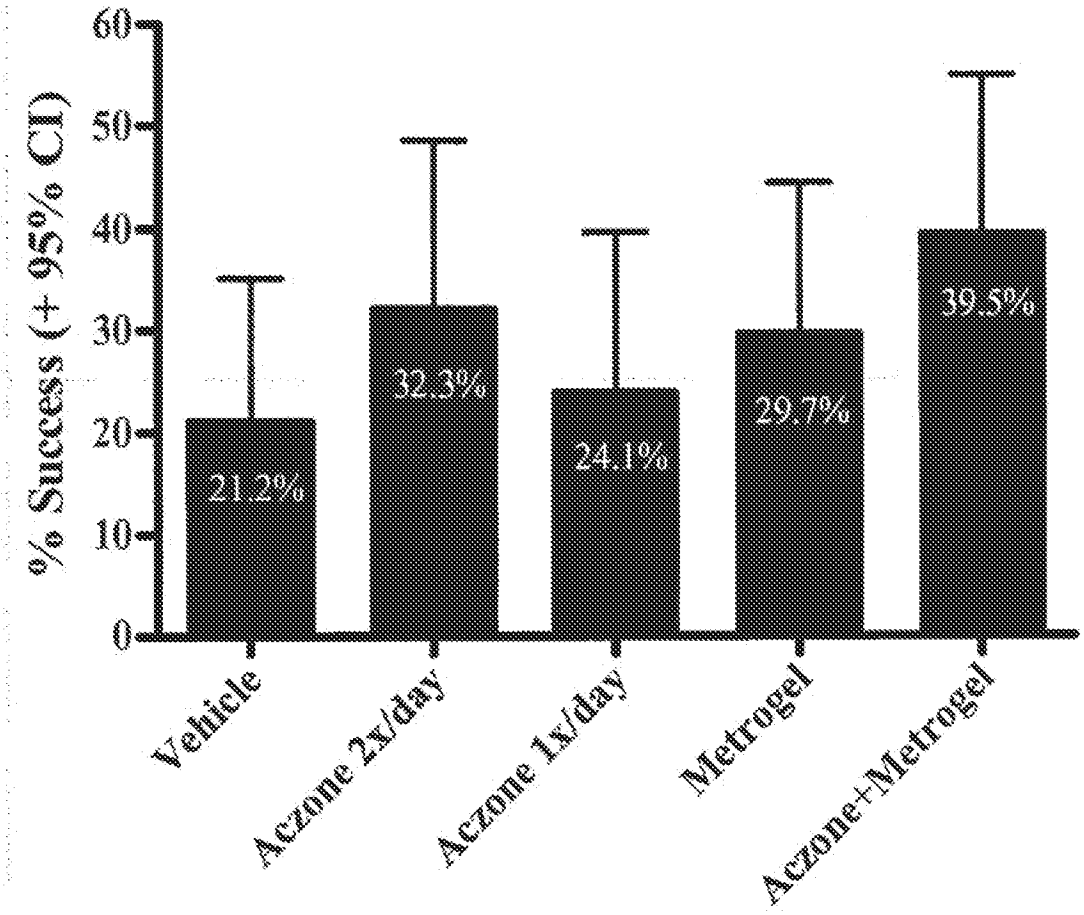
% Success (+ 95% CI)
60
50
40
30
20
10
0
21.2%
32.3%
24.1%
29.7%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

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], [0061]	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		90
—	US 2007/0281984 A1 (DOLPI et al) 06 December 2007 (06.12.2007), esp para [0010],[0037], [0038]	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		
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		97,100
—	WO 2005/016296 A1 (LATHROP et al) 24 February 2005 (25.02.2005), esp (page 1, ln 25-28),	
Y	and (page 1, ln 25-28)	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

Form PCT/ISA/210 (second sheet) (April 2007)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2011 (03.02.2011)

PCT

(10) International Publication Number
WO 2011/014627 A1

(51) International Patent Classification:
A61K 9/06 (2006.01) *A61K 9/00* (2006.01)
A61K 31/136 (2006.01) *A61P 17/10* (2006.01)
A61K 31/192 (2006.01)

(21) International Application Number:
PCT/US2010/043671

(22) International Filing Date:
29 July 2010 (29.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/229,903 30 July 2009 (30.07.2009) US

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(75) **Inventors/Applicants** *(for US only)*: **AHLUWALIA, Gurpreet** [US/US]; 3131 Michelson Drive, #303, Irvine, California 92612 (US). **WARNER, Kevin, S.** [US/US]; 1281 N. Walden Lane, Anaheim, California 92807 (US). **CHEN, Haigang** [CN/US]; 1962 Lansdowne Way, Petaluma, California 94954 (US). **YANG, Meidong** [CN/US]; 1400 Pinnacle Court, #204, Richmond, California 94801 (US).

(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-a	3	4	3.1-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	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	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 tretinion 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% 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	15 20
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 ceflulose 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
Dilute 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
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

2

Form PCT/ISA/210 (second sheet) (April 2005)

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
Y	WO 2006/048747 A1 (GLENMARK PHARMACEUTICALS LTD [IN]; CHAUDHARI G N [IN]; KHACHANE V S [I) 11 May 2006 (2006-05-11) page 17; table 1	1-20
Y	WO 2008/017914 A2 (AHUMADA AYALA FERNANDO [MX]) 14 February 2008 (2008-02-14) page 8	1-20
Y	"32258" In: Bundesverband der Pharmazeutischen Industrie: "Rote Liste 2002" 1 January 2002 (2002-01-01), Rote Liste Service GmbH , Frankfurth/Main , XP002606247 the whole document	1-20
X,P	US 2010/029781 A1 (MORRIS JEROME A [US]) 4 February 2010 (2010-02-04) page 4, left-hand column, paragraph 2 claims 1-20	1-20
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

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
US 2007122435 A1	31-05-2007	NONE	
WO 2006048747 A1	11-05-2006	AU 2005300313 A1	11-05-2006
		BR PI0517640 A	14-10-2008
		CA 2586821 A1	11-05-2006
		EP 1841416 A1	10-10-2007
		KR 20070091613 A	11-09-2007
		NZ 555336 A	24-12-2009
		US 2008075776 A1	27-03-2008
		ZA 200704467 A	30-07-2008
WO 2008017914 A2	14-02-2008	EP 2049068 A2	22-04-2009
		US 2009318371 A1	24-12-2009
US 2010029781 A1	04-02-2010	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER, KEVIN S
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	19107-US-AP

U.S.PATENTS Remove

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	

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	1	20060204526		2006-09-14	Lathrop et al	

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	1							☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LARD/ (03/17/2014)

/Leslie A. Royds Draper/ (03/17/2014)

Receipt date: 12/13/2013	Application Number	14082955 14082955 - GAU: 1629
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2013-11-18
	First Named Inventor	WARNER, KEVIN S
	Art Unit	1629
	Examiner Name	TBD
	Attorney Docket Number	19107-US-AP

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Examiner Signature	/Leslie A. Royds Draper/ (03/17/2014)	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/ (03/17/2014)

WEST Search History for Application 14082955

Creation Date: 2014031718:25

Prior Art Searches

Query	DB	Op.	Plur.	Thes.	Date
(dapson$2) and ("DGME" "diethylene glycol monoethyl ether")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and ("propylene glycol")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and (adapalen$2)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and ("methylparaben" "methyl paraben")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
(dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")) and ("propylene glycol") and (adapalen$2) and ("methylparaben" "methyl paraben") and ("sodium hydroxide" "NaOH" triethanolamin$2) and ("EDTA")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")) and (("propylene glycol") or (adapalen$2) or ("methylparaben" "methyl paraben") or ("sodium hydroxide" "NaOH" triethanolamin$2) or ("EDTA"))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")).ti, ab, clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014

(((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")).ti, ab, clm.) and (("propylene glycol") or (adapalen$2) or ("methylparaben" "methyl paraben") or ("sodium hydroxide" "NaOH" triethanolamin$2) or ("EDTA"))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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)	03/18/14	LARD
WEST Search (See Attached Search History)	03/18/14	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	18 March 2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: : Kevin S. Warner et al.	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Draper, Leslie A Royds
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

TRACK I – EXPEDITED EXAMINATION

RESPONSE TO NON-FINAL OFFICE ACTION DATED MARCH 21, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

The following is an amendment and response to the Non-Final Office Action mailed March 21, 2014.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims

The following claims replace all prior claims presented in this application.

1. (Currently amended) A **topical pharmaceutical** composition comprising**:**

about 7.0% w/w to about 8.0% w/w dapsone **as the sole active agent;**

~~**, a first solubilizing agent which is**~~ **about 25% w/w to about 35% w/w** diethylene glycol monoethyl ether**;** ~~**, optionally at least one second solubilizing agent,**~~

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 dapsone is present in the composition at a concentration of about 3% w/w to about 10% w/w**~~.

2. (Canceled)

3. (Currently amended) The composition of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about ~~**25%**~~ **30%** w/w.

Claims 4-11. (Canceled)

12. (Original) The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

13. (Original) The composition of claim 1, further comprising methyl paraben.

Claims 14-17. (Canceled)

18. (Withdrawn) A method for treating a dermatological condition comprising administering to a subject in need thereof a therapeutically effective amount of a composition of claim 1.

19. (Withdrawn – currently amended) The method of claim ~~**31**~~ **18** wherein the condition is *acne* ~~**vulgaris**~~ ***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.

20. (Withdrawn – currently amended) The method of claim ~~32~~ **19** wherein the condition is *acne* ~~**vulgaris**~~ ***vulgaris***.

21. (New) The composition of claim 1, wherein the dapsone is present in the composition at a concentration of about 7.5% w/w.

22. (New) A topical pharmaceutical composition comprising:

about 7.5% w/w dapsone as the sole active agent;

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.

23. (New) The composition of claim 22, further comprising methyl paraben.

24. (New – withdrawn) A method of treating a dermatological 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 in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of the composition of claim 22.

25. (New – withdrawn) The method of claim 24, wherein the condition is *acne vulgaris*.

REMARKS/ARGUMENTS

Claims 1-20 were pending in the application. Of these, claims 8, 9, and 18-20 have been withdrawn from consideration as the result of a restriction requirement.

In the present Amendment, Applicant has amended claims 1, 3, 19, and 20; canceled claims 2, 4-11, and 14-17; and added new claims 21-25. All of the claim amendments and new claims are fully supported by the specification as filed, and no new matter has been added.

Support for the recitation of "topical" in claim 1 (referring to topical pharmaceutical composition) can be found for example in the title on page 1 of the specification, and in paragraphs [004] (pages 1-2 of the specification), [005], [006] (page 2 of the specification), and [009] (pages 2-3 of the specification) (referring to "topical" application/medication). Support for the recitation of "pharmaceutical" in claim 1 can be found for example in paragraphs [009] (pages 2-3 of the specification), [0013] (page 3 of the specification, and in the abstract (page 21 of the specification) (referring to pharmaceutical products).

Support for the recitation of "about 7.0% w/w to about 8.0% w/w dapsone" in claim 1 can be found, for example, in the last sentence of paragraph [026], page 7 of the specification.

Support for the recitation of "dapsone as the sole active agent" in claim 1 can be found, for example, in paragraphs [004] (pages 1-2 of the specification; referring to "active agent" for acne) and [008] (page 2 of the specification, referring to dapsone as an anti-inflammatory agent useful in treating, e.g., *acne vulgaris*); in Table 1 (page 15 of the specification, where dapsone is listed as the sole active agent); and in paragraph [009] (page 3, referring to dapsone and dapsone/adapalene compositions useful for treating a variety of dermatological condition).

Support for the recitation of "about 25% w/w to about 35% w/w diethylene glycol monoethyl ether" in claim 1 can be found, for example in paragraph [0028] (page 7 of the specification).

Support for the recitation of "about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyltaurate copolymer" in claim 1 can be found, for example, in original claims 10 and 11.

Support for new claim 22 can be found, for example in Table 1 (page 15 of the specification).

Claim Rejections under 35 U.S.C. § 112

On pages 3-4 of the Action, claims 1-5, 7 and 16-17 stand rejected under 35 U.S.C. 112 (b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly 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. The rejection refers to claim 13-17; however it is believed that the Examiner means claims 16-17 as no grounds for rejection of claims 13-15 have been provided by the Examiner.

This rejection is rendered moot by deletion of the term "optionally" in claim 1, and by cancellation of claims 5, 7, and 16-17.

Rejections under 35 U.S.C. § 102

On pages 4-5 of the Action, claims 1-3, 6-7 and 13-16 stand rejected under 35 U.S.C. 102(a)(1) as allegedly being anticipated by Lathrop et al. (U.S. Patent Application Publication No. 2006/0204526), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) to show a fact.

On pages 5-6 of the Action, claims 1-7 and 11-17 stand rejected under 35 U.S.C. 102(a)(1) as allegedly being anticipated by Ahluwalia et al. (WO 2011/014627;) citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) to show facts.

The above rejections are deemed overcome in view of the present claim amendments, which incorporate the limitations of original claim 10. As original claim 10 has not been rejected under anticipation, the present anticipation rejection is deemed overcome.

Rejections under 35 U.S.C. § 103

On pages 6-9 of the Action, claims 1-7 and 10-17 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Ahluwalia et al. (WO 2011/014627 A1; February 2011; hereinafter "Ahluwalia"), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) and Garrett (WO 2009/108147 A1; 2009) to show facts, in view of Hani et al., (WO2010/105052 A1; hereinafter "Hani").

The Examiner cites Ahluwalia for allegedly teaching compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (referring to abstract). The Examiner refers to Ahluwalia teaching that dapsone/adapalene compositions preferably contain, *inter alia*, 0.5-10% w/w dapsone and 0.1-0.3% w/w adapalene, as well as 1-50% w/w diethylene glycol monoethyl ether and 1-8% w/w hydroxyethyl cellulose as a thickener (Table 1, p.8).

The Examiner cites Lubrizol for allegedly teaching that CARBOPOL 980 is a polymeric thickener synonymous with "carbomer homopolymer type C".

The Examiner cites Garrett for allegedly teaching that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether.

The Examiner acknowledges that Ahluwalia does not expressly teach (1) the claimed range of dapsone; (2) the claimed range of diethylene glycol monoethyl ether; (3) the claimed range of the polymeric viscosity builder; or (4) the use of acrylamide/sodium acryloyldimethyltaurate copolymer as the polymeric viscosity builder.

However, the Examiner asserts that Ahluwalia clearly teaches the use of the various components in amounts that clearly meet or encompass the ranges specifically recited in the present claims, and that 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 Ahluwalia within the disclosed ranges therein, and the selection of optimal amounts of components of the composition would have been a routine matter of optimization on the part of the artisan of ordinary skill.

The Examiner cites Hani for allegedly teaching that acrylamide/sodium acryloyldimethyltaurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p. 24-28, para [0018]; abstract).

The Examiner asserts that a person of ordinary skill in the art before the effective date of the claimed invention would have had a reasonable expectation of success in substituting the hydroxyethyl cellulose thickener of the dapsone/adapalene formulations described in Ahluwalia with acrylamide/sodium acryloyldimethyl taurate copolymer because each was well known in the art to be a suibable thickening agent for topical personal care products as evidenced by Ahluwalia and Hani.

Applicant respectfully disagrees with the Examiner's position and traverses this rejection. Applicant contends that the cited references alone or in combination do not teach or suggest all the claim limitations.

In *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1 (1966), the court set out a framework for applying the statutory language of § 103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248 (1851), and its progeny. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). It is an objective analysis.

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

It is well settled that *Graham v. John Deere Co.* is to be followed in the consideration and determination of obviousness under 35 U.S.C. § 103. In doing so, four factual inquiries are made:

(1) Determining the scope and contents of the prior art;

(2) Ascertaining the differences between the prior art and the claims in issue;

(3) Resolving the level of ordinary skill in the pertinent art; and

(4) Evaluating relevant evidence of secondary considerations.

When applying 35 U.S.C. § 103, the following basic considerations of law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention, and (4) reasonable expectation of success is the standard with which obviousness is determined. MPEP 2141-45, 8th ed., 2007 (*Hodosh* v. *Block Drug Co.,* 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 827 (1986)).

To reach a proper determination under 35 U.S.C. § 103, the Examiner must view all factual information and then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. *Gillette Co.* v. *S.C. Johnson & Son, Inc.,* 919 F.2d 720, 724 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F.2d 443, 449 (Fed. Cir. 1986), *cert. denied,* 484 U.S. 823 (1987). The law is quite clear that all of the evidence must be considered, not simply that which supports the Examiner's position.

In particular, to avoid hindsight analysis, a court "flexibly seeks evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination." *Rolls-Royce, PLC. v. United Techs. Corp.*, 2010 U.S. App. LEXIS 9201 at *27-*28 (Fed. Cir. May 5, 2010); *see e.g., Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1363-68 (Fed. Cir. 2008).

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference or to combine reference teachings. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.*

As instructed by the Supreme Court in *KSR*, an invention may be obvious if it would have been obvious to a person of ordinary skill to try a particular course of conduct. In particular, the Supreme Court stated that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue known options within his or her technical grasp. *KSR*, 550 U.S. at 420. Consistent with the Supreme Court's instruction, the Federal Circuit has described at least two classes where this reasoning does not apply. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

First, an invention would not be obvious or obvious to try when the ordinary artisan would have to try all possibilities in a field without any direction by the prior art. *Id.* "When 'what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful' and invention would not have been obvious." *Id.* (quoting *O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

This reasoning is consistent with *KSR*'s requirement that there be a "finite number of identified….solutions" and the number of options to be "small or easily traversed." *Id.*[1] Second, an invention is not obvious or obvious to try where the prior art does not guide the ordinary artisan toward a particular solution. *Id.* This reasoning is

[1] For example, in *In re Omeprazole patent Litig. v. Apotex Corp.,* 536 F.3d 1361 (Fed. Cir. 2008), the Federal Circuit gave considerable weight to the fact that even if one ordinarily skilled in the art would have recognized a particular problem, such a person would have been faced with multiple paths to solving the problem and would have been more likely to have chosen a solution different from the claimed invention in light of the known characteristics of the subject matter. In light of this, the Federal Circuit upheld the finding of nonobviousness of the district court.

consistent with *KSR*'s requirement that the solutions be predictable, and not otherwise an exploration of a general approach that seemed to be a promising field of experimentation. *Id*. The Federal Circuit has commented that "to the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *P&G v. Teva Pharms. USA, Inc.,* 566 F.3d 989, 996 (Fed. Cir. 2009) (quoting *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

At the outset, it is noted that Ahluwalia, the primary cited reference, does not disclose compositions comprising dapsone wherein dapsone is the sole active ingredient, as presently claimed. All of the formulations disclosed in Ahluwalia contain combinations of dapsone with adapalene, both of which are active ingredients. Thus Ahluwalia provides no motivation to one of ordinary skill in the art arrive at the presently claimed invention.

Garrett, while teaching a pharmaceutical composition comprising dapsone, wherein dapsone appears to be the sole active ingredient does not however teach or suggest using 7-8% w/w dapsone as presently claimed. Garrett refers to "CARBOPOL® 980" as a polymer thickener component (page 24, line 25 to page 25, line 13); however there is no mention of acrylamide/sodium acryloyldimethyltaurate copolymer as the sole thickener, as presently claimed.

While Hani refers to acrylamide/sodium acryloyldimethyltaurate copolymer as a thickener, this thickener is included as an additional thickener (in addition to PVP as a thickener; see below) in a laundry list of about 390 additional thickeners spanning more than three and half pages (Hani; pages 24-28). Furthermore, the composition in Hani is one that comprises at least one personal care acid or one pharmaceutical acid, and lightly to moderately crosslinked poly(N-vinyl-2-pyrrolidone) ("PVP"), which PVP provides thickening effects in acidic systems that are essentially stable (See Hani, paragraph [0001].

Unlike Hani, the composition of Garrett does not require the presence of one personal care acid or one pharmaceutical acid; nor does it require the presence of PVP as a thickener. Therefore, as the compositions of Garrett and Hani are distinct, Hani

provides no motivation to one of ordinary skill in the art having access to Garrett to substitute the "CARBOPOL® 980" of Garrett with the presently claimed acrylamide/sodium acryloyldimethyltaurate copolymer.

In view of the above, Applicant asserts that the presently claimed composition is not obvious in view of the cited references, alone or in combination.

The presently claimed compositions also have **unexpected advantages**. **The presently claimed compositions provide improved aesthetics (i.e., reduction in particle size which minimizes "gritty" feeling upon application)**.

As set forth in paragraph [010] (page 3 of the present application):

> [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).

Furthermore, as set forth in Example 1 (paragraph [042]; page 14 of the specification):

> [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).

Thus, Formulation # ENA in Table 1 which comprises 4% acrylamide/sodium acryloyldimethyltaurate copolymer thickener has smaller crystals/smaller particle size than Formulation # ENC which comprises 1% Carbomer homopolymer type C thickener, with the result that Formulation # ENA has better aesthetics (less "gritty" feeling upon application). **Therefore the composition comprising the acrylamide/sodium acryloyldimethyltaurate copolymer thickener has unexpected advantages over a composition where the thickener/viscosity builder is Carbomer homopolymer type C**.

Both amended claim 1 and new claim 22 cover the Formulation # ENA in Table 1. Amended claim 1 is similar to new claim 22 except that the level of dapsone in claim 1 ranges from about 7% w/w to about 8% w/w, and the level of viscosity builder in claim 1 ranges from about 2% w/w to about 6% w/w. In view of the showing of unexpected advantages at 7.5% dapsone and 4% polymeric viscosity builder (Table 1; Formulation # ENA), Applicant believes claim 1 is reasonably commensurate in scope what is disclosed in the specification.

In view of the reasons set forth above (traversing the allegation of *prima facie* obviousness and the showing of unexpected results), Applicants respectfully submit that the presently claimed compositions are non-obvious in view of the cited references, and respectfully requests the Examiner to withdraw the present rejection.

Request for Rejoinder

As set forth on pages 7-8 in the Restriction Requirement of January 22, 2014, the Examiner has required restriction between product claims and process claims. Where Applicant elects claims directed to product, as here, and the product claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product claims should be considered for rejoinder. Accordingly Applicant respectfully requests rejoinder of presently withdrawn claims 18-20. Applicant

would incorporate all the limitation of any allowed product claims into these process claims.

CONCLUSION

The above is believed to be a complete response to each and every ground of rejection as set for the in the Action dated March 21, 2014. The Examiner is respectfully invited to call the undersigned attorney to discuss any aspect of the present response to expedite prosecution and allowance of this case. If any fees are deemed due in connection with the filing of this Amendment, the Office is authorized to charge said fees Deposit Account 01-0885 or to credit any overpayment.

Respectfully submitted,

Dated: May 20, 2014

/Krishna G. Banerjee/
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Electronic Acknowledgement Receipt

EFS ID:	19076501
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Krishna G. Banerjee/Krishna Banerjee
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	20-MAY-2014
Filing Date:	18-NOV-2013
Time Stamp:	12:54:10
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		19107US_Resp_OA_052014.pdf	147748 866700307c3c1d951be66f779f2d35d3a66270be	yes	13

	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	13
Warnings:			
Information:			
	Total Files Size (in bytes):	147748	

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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/082,955	Filing Date 11/18/2013	☐ 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 **05/20/2014**

	(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
/MARGARET BYARS/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)

CONFIRMATION NO. 1222

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

PUBLICATION NOTICE

OC00000068595947

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

Publication No.US-2014-0142184-A1
Publication Date:05/22/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 06/11/2014

ALLERGAN, INC.
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EXAMINER	
DRAPER, LESLIE A ROYDS	
ART UNIT	**PAPER NUMBER**
1629	

NOTIFICATION DATE	DELIVERY MODE
06/11/2014	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. 14/082,955	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 *20 May 2014*.

☐ 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) *1,3,12,13 and 18-25* is/are pending in the application.

5a) Of the above claim(s) *18-20,24 and 25* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3,12,13 and 21-23* is/are rejected.

8)☐ Claim(s) _____ 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, 3, 12-13 and 18-25 are presented for examination.

Applicant's Amendment filed May 20, 2014 has been received and entered into the present application.

Claims 1, 3, 12-13 and 18-25 are pending. Claims 21-25 are newly added. Claims 2, 4-11 and 14-17 are cancelled. Claims 1, 3 and 19 are amended. Claims 18-20 and 24-25 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b), as being directed to non-elected process claims. Claims 1, 3, 12-13 and 21-23 are under examination and considered on their merits.

Applicant's arguments, filed May 20, 2014, 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.

Claim Rejections - 35 USC § 112(b) (New Grounds of Rejection)

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, 3, 12-13 and 21-23 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.

In claims 1 and 22, the indication that dapsone is "the sole active agent" renders the claim indefinite because it is unclear what "activity" of other agents is eliminated by this phrase. The limiting effect that this phrase is intended to have on the claim is further complicated by the fact that the other

components of the claim (e.g., diethylene glycol monoethyl ether, acrylamide/sodium acryloyldimethyl taurate copolymer, water) each are "active" as, respectively, a solubilizer, a polymeric viscosity builder, or a solubilizer. As a result, it is unclear how the phrase "sole active agent" is intended to limit the claim when the additional recited agents are also "active". Clarification is required.

In claims 1 and 22, there is insufficient antecedent basis for the term “the sole active agent”. Clarification is required.

As claims 3, 12-13, 21 and 23 depend variously from independent claims 1 and 22 and do not clarify these points of confusion, they must also be rejected on these same grounds.

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

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

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, 3, 12-13 and 21-23 are rejected under 35 U.S.C. 103 as being unpatentable over Ahluwalia et al. (WO 2011/014627 A1; February 2011) in view of Hani et al. (WO 2010/105052 A1; 2010), citing to Garrett (WO 2009/108147 A1; 2009), Villa (U.S. Patent No. 7,531,694; 2009) and Dreno (U.S. Patent Application Publication No. 2010/0130613; 2010) to show facts.

Ahluwalia et al. teaches topical compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (abstract). Ahluwalia et al. teaches that dapsone/adapalene compositions preferably contain, *inter alia*, 0.5-10% w/w dapsone, as well as 1-50% w/w diethylene glycol monoethyl ether, 1-8% w/w hydroxyethyl cellulose as a thickener, and 0.1-0.3% w/w methyl paraben (Table 1, p.8). Ahluwalia et al. teaches the following exemplary compositions:

(i) Table 2A teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 10% w/w or 20% w/w propylene glycol; 0.01% w/w EDTA; 0.75% w/w CARBOPOL 980; sodium hydroxide; and purified water;

(ii) Table 2B teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w diethylene glycol monoethyl ether; 15% w/w propylene glycol; 0.01% w/w EDTA; 2% w/w hydroxyethyl cellulose (i.e., a polymeric thickener); sodium hydroxide; and purified water; and

(iii) Fig.5 (Compositions 1 and 2) teaches compositions of 5% w/w dapsone; 0.1% w/w or 0.3% w/w adapalene; 25% w/w TRANSCUTOL; 0.01% w/w EDTA disodium; 4% w/w hydroxyethyl cellulose (i.e., a polymeric thickener); sodium hydroxide; and water.

Garrett teaches that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether as recited in Applicant's instant claims 1, 3, and 22 (p.14, l.5-6).

Villa et al. teaches that dapsone is an antibacterial agent (col.1, l.10-16). Dreno teaches that adapalene is a retinoid that affects cell differentiation and exerts an anti-inflammatory effect (p.1, para.[0023]). As adapalene does not possess the same therapeutic activity as dapsone, it is, therefore, not patentably excluded from the instant claims as being another “active agent” with the same activity as dapsone. Note, further, that the claim as a whole does not patentably exclude additional, unrecited

elements (i.e., including adapalene), as the claim is defined using the open-ended transitional phrase "comprising". MPEP §2111.03.

Ahluwalia et al. 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% w/w to about 6% w/w" (claim 1), particularly about 4% w/w (claims 12 and 22) or (2) the claimed range of dapsone (i.e., "about 7.0% w/w to about 8.0% w/w" or "about 7.5% w/w"; claims 1 and 21-22) or the claimed range of DGME (i.e., "about 25% w/w to about 35% w/w" or "about 30% w/w"; claims 1, 3 and 22).

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 hydroxyethyl cellulose thickener of the dapsone formulation described in Ahluwalia et al. as being advantageously incorporated in an amount of 1-8% w/w, particularly 2% w/w or 4% w/w, 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 Ahluwalia et al. 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 hydroxyethyl cellulose and acrylamide/sodium acryloyldimethyl taurate copolymer are 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 exemplified compositions of Ahluwalia et al. meet Applicant's recited amounts of dapsone and DGME, absent any clear definition of the amount of variation tolerated by the term "about" as used in the claims to define the endpoints of the recited range(s). For example, Ahluwalia et al. provides for

compositions in Fig.5 (Compositions 1 and 2) that comprise 5% w/w dapsone (i.e., which is "about 7.0% w/w to about 8.0% w/w" or "about 7.5% w/w" dapsone as recited in claims 1 and 21-22); 0.1% w/w or 0.3% w/w adapalene; 25% w/w TRANSCUTOL (i.e., DGME as claimed, which also is "about 30% w/w" DGME as recited in claims 3 and 22); 0.01% w/w EDTA disodium; 4% w/w hydroxyethyl cellulose; sodium hydroxide; and water. Applicant provides no direction in the specification or claims as originally filed as to the metes and bounds of the term "about" such that it would have been clear that, e.g., 5% w/w dapsone, as exemplified in Ahluwalia et al. would not have been within the scope of the claims as amended.

In further support of *prima facie* obviousness, note that the teachings in Ahluwalia et al. provide for ranges of dapsone, DGME and polymeric thickener (i.e., hydroxyethyl cellulose as used in Ahluwalia et al.) that clearly circumscribe the ranges instantly claimed. See, e.g., Ahluwalia et al. at p.8, Table 1, which discloses the use of 0.5-10% w/w dapsone, as well as 1-50% w/w diethylene glycol monoethyl ether and 1-8% w/w hydroxyethyl cellulose as a thickener (which clearly suggests the use of the same amount of another thickener, such as that of Hani et al.). Such ranges clearly encompass Applicant's instantly claimed ranges of:

(i) "about 7.0% w/w to about 8.0% w/w" dapsone (claim 1) or "about 7.5% w/w" dapsone (claims 21-22); or

(ii) "about 25% w/w to about 35% w/w" DGME (claim 1) or "about 30% w/w" DGME (claims 3 and 22).

Thus, Ahluwalia et al. clearly 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 Ahluwalia et al. within the disclosed ranges therein. This is because Ahluwalia et al. 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 Ahluwalia et al. 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.

Response to Applicant's Arguments

In reply, Applicant argues that Ahluwalia et al. "does not disclose compositions comprising dapsone wherein dapsone is the sole active ingredient" as claimed, as the formulations disclosed in Ahluwalia et al. all contain adapalene (Remarks, p.10). This argument has been fully considered, but is unpersuasive. Applicant's instant claims do not patentably exclude the incorporation of adapalene into the topical pharmaceutical composition because the claim, as a whole, remains open to the inclusion of additional, unrecited elements as evidenced by the use of the transitional phrase "comprising". MPEP §2111.03. In addition, even if one were to construe the claim as being limited to dapsone as "the sole active agent" (which the Examiner does not concede), the inclusion of adapalene is still not patentably excluded from the claim, as dapsone and adapalene function in clearly distinct ways (i.e., dapsone as an antibacterial agent, see Villa; adapalene as an anti-inflammatory agent that affects cell differentiation, see Dreon) and, thus, dapsone (even when combined with adapalene) remains the "sole active agent" that functions as an antibacterial agent.

Applicant alleges that Garrett "does not however teach or suggest using 7-8% w/w dapsone as presently claimed" and "Garrett refers to 'CARBOPOL 980' as a polymer thickener component" but that "there is no mention of acrylamide/sodium acryloyldimethyl taurate copolymer as the sole thickener" as

claimed (Remarks, p.10). This is unpersuasive. Garrett was solely relied upon for its factual teaching that TRANSCUTOL, as used in Ahluwalia et al., is synonymous with DGME (i.e., diethylene glycol monoethyl ether) as used in the instant claims. Garrett was cited only to demonstrate that this term used in the prior art of Ahluwalia et al. (i.e., TRANSCUTOL) was equivalent to a term used in the instant claims (i.e., DGME). Garrett was not cited for the purpose of demonstrating that any element of the claimed invention was *prima facie* obvious. Applicant's attempt to bodily incorporate the teachings of Garrett into that of Ahluwalia et al. (or any of the other references for that matter), therefore, is unavailing, as it overstates the relevance of Garrett in establishing the instant *prima facie* case of obviousness and fails to consider the purpose for which Garrett was cited.

In reference to Hani et al., Applicant alleges that the reference only teaches acrylamide/sodium acryloyldimethyl taurate copolymer as “an additional thickener” in addition to PVP and that it is disclosed "in a laundry list of about 390 additional thickeners spanning more than three and a half pages" (Remarks, p.10). The Examiner infers Applicant is arguing that, because Hani et al. employs other thickeners as part of his disclosed composition, that there is no reason to employ acrylamide/sodium acryloyldimethyl taurate copolymer alone, as instantly claimed.

This is unpersuasive for several reasons. First, Applicant is again attempting to bodily incorporate the features of Hani et al. into that of Ahluwalia et al., by alleging that Hani et al. uses a combination of thickeners, whereas the instant claims do not. However, Hani et al. was cited solely for its teaching that acrylamide/sodium acryloyldimethyl taurate copolymer is a suitable thickener/viscosity increasing agent for use in topical personal care products (p.24-28, para.[0118], abstract). The fact that it was used in Hani et al. as an additional thickening agent does not detract from its suitability as a thickener for other topical personal care products, even when used alone. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Second, even if it were true that Hani et al. did not teach or suggest that acrylamide/sodium acryloyldimethyl taurate copolymer could be used as a thickening component without PVP (which the Examiner does not concede), the argument would still be found unpersuasive because the instant claims are not expressly limited to acrylamide/sodium acryloyldimethyl taurate copolymer alone in the absence of other thickening agents. Applicant recites in, e.g., instant claim 1 "about 2% w/w to about 6% w/w of a polymeric viscosity builder consisting of acrylamide/sodium acryloyldimethyl taurate copolymer", but neglects to consider that the claim, as a whole, remains open to the inclusion of additional, unrecited elements, including other thickeners. This is clearly evidenced by Applicant's use of the open-ended transitional phrase "comprising" in l.1 of the claim. Similar rationale also applies to instant claim 22. MPEP §2111.03.

Third, Applicant appears to espouse the position that, because Hani et al. teaches acrylamide/sodium acryloyldimethyl taurate copolymer "in a laundry list of about 390 additional thickeners spanning more than three and a half pages", the selection of this particular thickener is not obvious. This is unpersuasive. MPEP §2123 states that ""[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004)." The fact that Hani et al. teaches other suitable thickeners does not teach away from the selection of any one or more such options in the recited list.

Furthermore, it is unclear how the fact that the art had identified hundreds of components that act as suitable thickeners or viscosity increasing agents for use in topical personal care products renders any particular thickener nonobvious. Hani et al. demonstrates that, at the time of the invention, the art of selecting thickeners for topical pharmaceutical formulations was crowded and well-characterized. Selecting any of the numerous art-recognized options as a thickener to include in the formulation of Ahluwalia et al. would have been considered routine optimization because it would have merely applied the well-known principle in the art of including a suitable thickening agent in a topical personal care formulation. Hani et al. provides clear evidence that the thickener art for topical formulations is advanced, and skilled artisans have identified numerous functional equivalents. Applicant is in effect advocating that

as a field of art becomes advanced, any given option within that field becomes less obvious. That rule, however, contradicts the principles that underlie the obviousness analysis. It cannot be the case that inventions in more investigated arts become less obvious simply because skilled artisans have identified a larger number of acceptable options within the art's practices. A field of endeavor does not become less predictable as it becomes increasingly well-understood.

Applicant urges that the "compositions of Garrett and Hani are distinct" and, therefore, "Hani provides no motivation to one of ordinary skill in the art having access to Garrett to substitute the CARBOPOL 980 of Garrett with the presently claimed acrylamide/sodium acryloyldimethyl taurate copolymer" (Remarks, p.10-11). This is unpersuasive, as it is a patent mischaracterization of the grounds of rejection. In the instant case, Ahluwalia et al. exemplifies topical formulations of dapsone, into which 4% w/w hydroxyethyl cellulose was incorporated as a thickening agent. Hani et al. teaches that acrylamide/sodium acryloyldimethyl taurate copolymer, as used in the instant claims, was a known thickener/viscosity increasing agent suitable for use in topical personal care formulations (p.24-28, para.[0118], abstract). The art, therefore, clearly establishes that hydroxyethyl cellulose and acrylamide/sodium acryloyldimethyl taurate copolymer were known functional equivalents and, thus, the substitution of one for the other would have been *prima facie* obvious to the skilled artisan before the effective filing date of the invention. Garrett, however, was not cited for the purpose of demonstrating that any element of the claimed invention was *prima facie* obvious, but rather was solely relied upon for its factual teaching that TRANSCUTOL, as used in Ahluwalia et al., is synonymous with DGME (i.e., diethylene glycol monoethyl ether) as used in the instant claims.

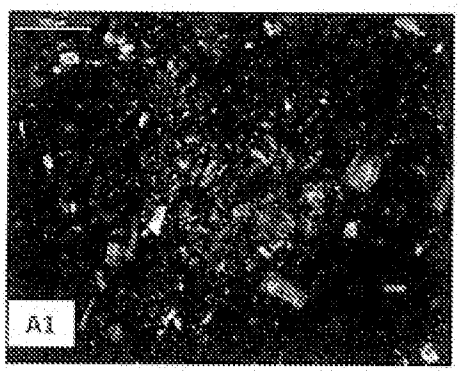
Finally, Applicant urges that the "presently claimed compositions have unexpected advantages" in the form of "improved aesthetics" as evidenced by a "reduction in particle size which minimizes 'gritty' feeling upon application" (Remarks, p.11). Applicant cites to Ex.1 (para.[042], p.14) as evidence of the two tested formulations and the effect of the thickening agent on particle size. Applicant also cites to Fig.2 to provide microscopic images demonstrating this difference in particle size. Applicant urges that the instant claims are "reasonably commensurate in scope with what is disclosed in the specification" (Remarks, p.12).

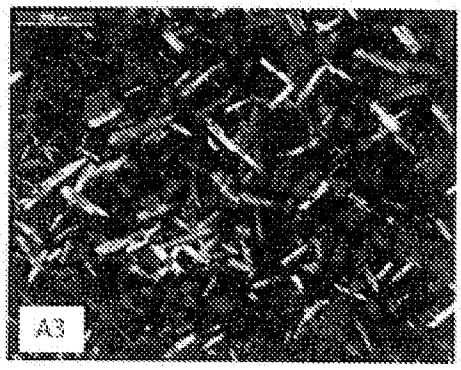
The data has been fully considered, but fails to be probative of nonobviousness, as none of the instant claims are actually commensurate in scope with the tested formulation. Table 1 provides two formulations, ENA and ENC (p.15, para.[042]). ENA, understood to be representative of Applicant's claimed formulation, contains 7.5% w/w dapsone, 30% w/w DGME, 4% acrylamide/sodium acryloyldimethyl taurate copolymer, 0.2% w/w methyl paraben, pH adjusting solution to provide pH of 5.5-7.0, and purified water. ENC is substantially similar, but for the fact that the 4% w/w acrylamide thickener was replaced by 1% w/w carbomer homopolymer type C. The instant claims, however, are not limited to this single exemplified amount of 7.5% w/w (claim 1, e.g., comprises "about 7.0% w/w to about 8.0% w/w" dapsone), 30% w/w DGME (claim 1, e.g., comprises "about 25% to about 35% w/w" DGME), 4% w/w acrylamide/sodium acryloyldimethyl taurate copolymer (claim 1, e.g., comprises "about 2% w/w to about 6% w/w" of this copolymer). In addition, ENA comprises additional components (0.2% w/w methyl paraben and pH adjusting solution to provide pH 5.5-7.0), none of which are required by the broadest embodiments of the claims. Note that claim 22 suffers from similar issues, in that the claimed amounts are each defined using the term "about", which permits for values outside of the recited numerical value and, therefore, is not strictly commensurate in scope with the tested formulation.

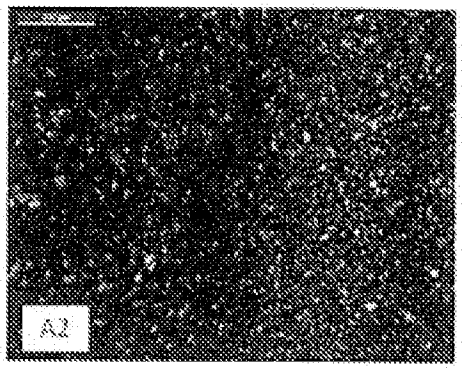
Even if the instant claims were amended to be commensurate in scope with the tested ENA formulation (which the Examiner does not concede), the proffered data would still fail to be probative of nonobviousness because the difference in polymeric thickening agent is not the sole difference between the ENA and ENC formulations. Comparative formulation ENC contains one fourth of the amount of thickening agent than that used in ENA (i.e., 1% w/w carbomer homopolymer type C in ENC as compared to 4% w/w acrylamide/sodium acryloyldimethyl taurate copolymer in ENA). Applicant fails to account for this discrepancy in concentration, instead ascribing this alleged difference in particle size solely to the selection of thickener, without addressing how the difference in concentration would have affected crystallization of dapsone and, thus, had an alleged effect on particle size of the composition.

In addition, though Applicant urges that Fig.2 provides microscopic evidence of this difference in particle size between the ENA and ENC formulations, the images proffered in Fig.2 cannot be afforded the significance that Applicant urges because it is wholly unclear which image is relevant to which of the

tested formulations. Fig.2 simply presents "[p]olarized light images of dapsone in suspension formulations", with corresponding figures A1, A2, A3 and A4:







, but it is wholly unclear from what formulation each of the images has been generated. Applicant's Fig.2, therefore, fails to provide clear documentation of this alleged unexpected difference in particle size of the tested formulations ENA and ENC.

Still further, even if Applicant had clearly demonstrated a difference in particle size between the ENA and ENC formulations (which the Examiner does not concede), the proffered data would still fail to be clearly germane to patentability because it fails to establish that the difference in properties is, in fact, unexpected and unobvious and of both statistical and practical significance. MPEP §716.02(b)(I). In order to be probative, a showing of unexpected results must necessarily be accompanied by a clear indication of what the skilled artisan would have expected, as well as a clear showing of how the claimed invention exceeds such expectations so as to provide properties or results that were unexpected, unobvious and of statistical and practical significance. Note, further, that Applicant has failed to clearly explain how this

property of particle size (and, thus, texture) actually affects the composition so as to clearly translate into an "unexpected advantage" not found in prior art compositions. Applicant is reminded that he, not the Office, bears the burden of explaining data proffered as evidence of nonobviousness. MPEP §716.02(b).

For these reasons *supra*, rejection of claims 1, 3, 12-13 and 21-23 is proper.

Conclusion

Rejection of claims 1, 3, 12-13 and 21-23 is proper.

Claims 18-20 and 24-25 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

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 (MPEP §714.02 and §2163.06). Note that support should be provided for amendments to previously pending claims, as well as any newly added claims. In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, not the published application. Due to the procedure outlined in MPEP §2163.06 for interpreting claims, it is noted that 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.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). 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 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

June 5, 2014

Notice of References Cited	Application/Control No. 14/082,955	Applicant(s)/Patent Under Reexamination WARNER ET AL.	
	Examiner Leslie A. Royds Draper	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,531,694	05-2009	Villa et al.	568/28
*	B	US-2010/0130613	05-2010	DRENO, Brigitte	514/569
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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)	03/18/14	LARD
WEST Search (See Attached Search History)	03/18/14	LARD
Updated Inventor Search (PALM Database, eDAN)	06/05/14	LARD
Updated WEST Search (See Attached Search History)	06/05/14	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	05 June 2014

WEST Search History for Application 14082955

Creation Date: 2014060511:05

Prior Art Searches

Query	DB	Op.	Plur.	Thes.	Date
(dapson$2) and ("DGME" "diethylene glycol monoethyl ether")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and ("propylene glycol")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and (adapalen$2)	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether")) and ("methylparaben" "methyl paraben")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
(dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")	PGPB, USPT, USOC, EPAB, JPAB, DWPI,	OR	YES		03-17-2014

	TDBD, FPRS				
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")) and ("propylene glycol") and (adapalen$2) and ("methylparaben" "methyl paraben") and ("sodium hydroxide" "NaOH" triethanolamin$2) and ("EDTA")	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")) and (("propylene glycol") or (adapalen$2) or ("methylparaben" "methyl paraben") or ("sodium hydroxide" "NaOH" triethanolamin$2) or ("EDTA"))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")).ti, ab, clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
(((dapson$2) and ("DGME" "diethylene glycol monoethyl ether" "ethoxydiglycol" "ethoxy diglycol")).ti, ab, clm.) and (("propylene glycol") or (adapalen$2) or ("methylparaben" "methyl paraben") or ("sodium hydroxide" "NaOH" triethanolamin$2) or ("EDTA"))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		03-17-2014
(dapson$2) and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014
((dapson$2) and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))) and ($acrylamid$2)	PGPB, USPT, USOC, EPAB,	OR	YES		06-05-2014

	JPAB, DWPI, TDBD, FPRS				
((dapson$2) and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))) and (($acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014
((dapson$2) and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))) and ((acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014
(dapson$2).ti, ab, clm.	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014
((dapson$2).ti, ab, clm.) and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014
((dapson$2).ti, ab, clm. and ("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) "TRANSCUTOL" (ethoxy adj2 diglycol))) and (($acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2))	PGPB, USPT, USOC, EPAB, JPAB, DWPI, TDBD, FPRS	OR	YES		06-05-2014

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
19107 (AP)	14/082,955	November 18, 2013
First Named Inventor:	**Title:**	
Kevin S. Warner	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
   - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
   - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
     - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
     - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
       - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
       - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Krishna G. Banerjee/	August 21, 2014
Name (Print/Typed) Krishna G. Banerjee	Practitioner Registration No. 43,317

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

[✓] * Total of 1 forms are submitted.

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner et al.	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Draper, Leslie A Royds
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

RESPONSE TO FINAL OFFICE ACTION DATED JUNE 11, 2014 - REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE – RESPONSE BEING FILED UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

The following is an amendment and response to the Final Office Action mailed June 11, 2014. Applicant respectfully notes that this is a reply under 37 CFR 1.116 and therefore respectfully requests expedited processing and reply by the Examiner in accordance with the provisions and time periods described in MPEP 714.13(V). Applicant is concurrently filing a Certification and Request for Consideration under the After Final Consideration Pilot Program 2.0.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims

The following claims replace all prior claims presented in this application.

1. (Currently amended) A topical pharmaceutical composition comprising:

about 7.0% w/w to about 8.0% w/w dapsone ~~**as the sole active agent**~~;

about 25% w/w to about 35% 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**.

2. (Previously canceled)

3. (Previously presented) The composition of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

Claims 4-11. (Previously canceled)

12. (Original) The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

13. (Original) The composition of claim 1, further comprising methyl paraben.

Claims 14-17. (Previously canceled)

Claims 18-20. (Canceled)

21. (Previously presented) The composition of claim 1, wherein the dapsone is present in the composition at a concentration of about 7.5% w/w.

22. (Currently amended) A topical pharmaceutical composition comprising:

about 7.5% w/w dapsone ~~**as the sole active agent**~~;

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 composition does not comprise adapalene**.

23. (Previously presented) The composition of claim 22, further comprising methyl paraben.

Claims 24-25. (Canceled)

26. (New) A topical pharmaceutical composition **for the treatment of acne,** comprising:

about 7.0% w/w to about 8.0% w/w dapsone;

about 25% w/w to about 35% 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 dapsone is the sole active agent for the treatment of acne in the composition.

27. (New) The composition of claim 26, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

28. (New) The composition of claim 26, further comprising methyl paraben.

29. (New) The composition of claim 26, wherein the dapsone is present in the composition at a concentration of about 7.5% w/w.

30. (New) A topical pharmaceutical composition **for the treatment of acne,** 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 dapsone is the sole active agent for the treatment of acne in the composition.

REMARKS/ARGUMENTS

The undersigned attorney thanks the Examiner for the courtesy extended to him to discuss this case through a phone interview on August 14, 2014,.

Claims 1-3, 12, 13, and 18-25 were pending in the application. In the present Amendment, Applicant has amended claims 1 and 22; canceled claims 18-20, and 24-25; and added new claims 26-29. All of the claim amendments and new claims are fully supported by the specification as filed, and no new matter has been added.

Support for the recitation "wherein the composition does not comprise adapalene" in amended claims 1 and 22, and for the recitation "for the treatment of acne" and "wherein the dapsone is the sole active agent for the treatment of acne in the composition" in new claims 26 and 30 can be found for example in Table 1 (page 15 of the specification, wherein only dapsone and no adapalene is used in the formulation); in paragraph [009], pages 2-3 (referring to dapsone and dapsone/adapalene compositions useful for treating a variety of dermatological condition, including acne); paragraph [006], page 2 of the specification (referring to a need for compositions and methods used in the treatment of acne); paragraph [008], page 2 of the specification (referring to the use of dapsone as an anti-inflammatory agent, and to its use to treat *acne vulgaris*); paragraph [004], pages 1-2 of the specification (referring to "active agent known to have anti-acne activity").

Claim Rejections under 35 U.S.C. § 112

On pages 2-3 of the Action, claims 1, 3, 12-13 and 21-23 stand rejected under 35 U.S.C. 112 (b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly 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.

The Examiner refers to the phrase "the sole active agent", and asserts that this phrase renders the term indefinite because it is unclear what "activity" of other agents is eliminated by phrase. The Examiner also asserts that there is insufficient antecedent basis for this term.

The phrase "sole active agent' is no longer used in currently amended claims 1 and 22; according this rejection is moot with respect to these claims, and claims dependent thereon, viz., claims 12-13, 21, and 23. In so far as this rejection is applied to new claims 26-30, Applicant traverses this rejection.

Claims 26 and 30 recite that "dapsone is the sole active agent for the treatment of acne in the composition". Thus the "activity" here clearly refers to the anti-acne activity of dapsone. The claim language also makes it clear, that other than dapsone, there is no other ingredient in the claimed composition that has "anti-acne" activity. The phrase "active agent" has the same meaning as "active ingredient (AI)"/ "active pharmaceutical ingredient (API)", and in conjunction with the phrase "for the treatment of acne" leaves no room for ambiguity that the "activity" here refers to the "anti-acne" activity. Applicant also does not find any lack of antecedent basis in claims 26-30.

Accordingly, Applicant respectfully requests the Examiner to withdraw the rejection.

Rejections under 35 U.S.C. § 103

On pages 3-7 of the Action, claims 1, 3, 12-13 and 21-23 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Ahluwalia et al. (WO 2011/014627 A1; February 2011; hereinafter "Ahluwalia") in view of Hani et al., (WO2010/105052 A1; hereinafter "Hani"), citing to Garrett (WO 2009/108147 A1; 2009), Villa (U.S. Patent 7,531,694; 2009), and Dreno (U.S. Patent Application Publication No. 2010/0130613; 2010) to show facts,.

The Examiner cites Ahluwalia for allegedly teaching compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (referring to abstract). The Examiner refers to Ahluwalia teaching that dapsone/adapalene compositions preferably contain, *inter alia*, 0.5-10% w/w dapsone and 0.1-0.3% w/w adapalene, as well as 1-50% w/w diethylene glycol monoethyl ether and 1-8% w/w hydroxyethyl cellulose as a thickener (referring to Table 1, p.8).

The Examiner cites Garrett for allegedly teaching that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether (referring to Garrett, p. 14, l. 5-6).

The Examiner cites Villa for allegedly teaching that dapsone is an antibacterial agent (col. 1, l. 10-16), and Dreno for allegedly teaching that adapalene is a retinoid that affects cell differentiation and exerts an anti-inflammatory effect (referring to p. 1, para. [0023]). The Examiner asserts that as adapalene does not possess the same therapeutic activity as dapsone, it is therefore, not patentably excluded from the instant claims as being another "active agent" with the same activity as dapsone.

The Examiner cites Hani for allegedly teaching that acrylamide/sodium acryloyldimethyltaurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p. 24-28, para [0018]; abstract).

The Examiner asserts that a person of ordinary skill in the art before the effective date of the claimed invention would have had a reasonable expectation of success in substituting the hydroxyethyl cellulose thickener of the dapsone formulation described in Ahluwalia as being advantageously incorporated in an amount of 1-8% w/w, particularly 2% w/w or 4% w/w, 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 Ahluwalia and Hani.

The Examiner concludes by asserting that Ahluwalia clearly teaches the use of every component recited the present composition in amounts that clearly meet or encompass the ranges specifically recited in the present claims, and that a person of ordinary skill in the art before the effective date of the claimed invention would have had a reasonable expectation of success in varying the amount of the components of the composition as described in Ahluwalia within the disclosed ranges therein.

Applicant respectfully disagrees with the Examiner's position and traverses this rejection. Applicant contends that the cited references alone or in combination do not teach or suggest all the claim limitations.

In *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1 (1966), the court set out a framework for applying the statutory language of § 103, language itself based on the

logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248 (1851), and its progeny. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). It is an objective analysis.

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

It is well settled that *Graham v. John Deere Co.* is to be followed in the consideration and determination of obviousness under 35 U.S.C. § 103. In doing so, four factual inquiries are made:

(1) Determining the scope and contents of the prior art;

(2) Ascertaining the differences between the prior art and the claims in issue;

(3) Resolving the level of ordinary skill in the pertinent art; and

(4) Evaluating relevant evidence of secondary considerations.

When applying 35 U.S.C. § 103, the following basic considerations of law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention, and (4) reasonable expectation of success is the standard with which obviousness is determined. MPEP 2141-45, 8th ed., 2007 (*Hodosh* v. *Block Drug Co.,* 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 827 (1986)).

To reach a proper determination under 35 U.S.C. § 103, the Examiner must view all factual information and then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. *Gillette Co.* v. *S.C. Johnson & Son, Inc.,* 919 F.2d 720, 724 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F.2d 443, 449 (Fed. Cir. 1986), *cert. denied,* 484 U.S. 823 (1987). The law is quite clear that all of the evidence must be considered, not simply that which supports the Examiner's position.

In particular, to avoid hindsight analysis, a court "flexibly seeks evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination." *Rolls-Royce, PLC. v. United Techs. Corp.*, 2010 U.S. App. LEXIS 9201 at *27-*28 (Fed. Cir. May 5, 2010); *see e.g., Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1363-68 (Fed. Cir. 2008).

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.*

As instructed by the Supreme Court in *KSR*, an invention may be obvious if it would have been obvious to a person of ordinary skill to try a particular course of conduct. In particular, the Supreme Court stated that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue known options within his or her technical grasp. *KSR*, 550 U.S. at 420. Consistent with the Supreme Court's instruction, the Federal Circuit has described at least two classes where this reasoning does not apply. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

First, an invention would not be obvious or obvious to try when the ordinary artisan would have to try all possibilities in a field without any direction by the prior art. *Id.* "When 'what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be

successful' and invention would not have been obvious." *Id.* (quoting *O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

This reasoning is consistent with *KSR*'s requirement that there be a "finite number of identified….solutions" and the number of options to be "small or easily traversed." *Id.*[1] Second, an invention is not obvious or obvious to try where the prior art does not guide the ordinary artisan toward a particular solution. *Id.* This reasoning is consistent with *KSR*'s requirement that the solutions be predictable, and not otherwise an exploration of a general approach that seemed to be a promising field of experimentation. *Id.* The Federal Circuit has commented that "to the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *P&G v. Teva Pharms. USA, Inc.,* 566 F.3d 989, 996 (Fed. Cir. 2009) (quoting *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

Present claims 1 and 22 clearly exclude adapalene from the scope of the claimed composition. Ahluwalia does not disclose or suggest a composition where adapalene is not an ingredient of the composition. Therefore , with respect to these claims, Ahluwalia, as the primary reference, alone or in combination with Hani, Garrett, Villa and Dreno, does not render obviously the composition of these claims.

With respect to new claims 26 and 30, again the cited references alone, or in combination do not teach or suggest the compositions claimed therein, wherein dapsone is the sole active agent for the treatment of acne in the composition. With regard to the Examiner's comments that the therapeutic activity of dapsone (referred to as an antibacterial agent in Villa) and adapalene (referred to as affecting cell differentiation and having an anti-inflammatory effect in Dreno) are different, Applicant notes that notwithstanding such effects or regardless of such effects, it is clear to one of

[1] For example, in *In re Omeprazole patent Litig. v. Apotex Corp.,* 536 F.3d 1361 (Fed. Cir. 2008), the Federal Circuit gave considerable weight to the fact that even if one ordinarily skilled in the art would have recognized a particular problem, such a person would have been faced with multiple paths to solving the problem and would have been more likely to have chosen a solution different from the claimed invention in light of the known characteristics of the subject matter. In light of this, the Federal Circuit upheld the finding of nonobviousness of the district court.

ordinary skill in the art that both adapalene and dapsone are anti-acne agents, i.e., they are active pharamaceutical ingredients suitable for the treatment of acne. As present claims 26 and 30 exclude any anti-acne agent other than dapsone, they are not rendered obvious in view of the cited references.

Applicants respectfully submit that the presently claimed compositions are not obvious in view of the cited references, and respectfully requests the Examiner to withdraw the present rejection.

CONCLUSION

The above is believed to be a complete response to each and every ground of rejection as set for the in the Action dated June 11, 2014. The Examiner is respectfully invited to call the undersigned attorney to discuss any aspect of the present response to expedite prosecution and allowance of this case. If any fees are deemed due in connection with the filing of this Amendment, the Office is authorized to charge said fees Deposit Account 01-0885 or to credit any overpayment.

Dated: August 21, 2014

Respectfully submitted,

/Krishna G. Banerjee/
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Registration No. 43,317
Attorney for Applicants

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Electronic Acknowledgement Receipt

EFS ID:	19934288
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Krishna G. Banerjee/Alexis Swan
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	21-AUG-2014
Filing Date:	18-NOV-2013
Time Stamp:	19:43:19
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	After Final Consideration Program Request	19107-Cert-and-Req-for-Consideration-after-FOA.pdf	226574 2d61c6fa6b6c3663dd75f47061ffc9f12bc269b5	no	2

Warnings:	
Information:	

2		19107-Resp-to-Final-OA-of-06-11-2014.pdf	126092 861377663badf1fa90c22e6c342e7bc9ebac497f	yes	10

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Response After Final Action	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	10

Warnings:	
Information:	
Total Files Size (in bytes):	352666

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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/082,955	Filing Date 11/18/2013	☐ 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	08/21/2014	(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))	* 4	Minus	***3	= 1	X $420 =	420
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	420

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
/MARY PEOPLES/

This collection of information is required by 37 CFR 1.16. 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, 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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 08/29/2014

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
08/29/2014	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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/082,955	WARNER ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds Draper	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Leslie A. Royds Draper (Primary Exr)*. (3)_____.

(2) *Krishna Banerjee (for Applicant)*. (4)_____.

Date of Interview: *14 August 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,3,12,13 and 21-23*.

Identification of prior art discussed: *Ahluwalia et al. as used in the 103(a) rejection*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

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

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant's representative discussed the pending rejection of the claims under 35 U.S.C. 103(a) and indicated that he wished to exclude adapalene from the topical pharmaceutical composition as claimed. The Examiner explained that the phrase "sole active agent" does not definitively exclude this component from the composition as claimed, as it is unclear what the "activity" of the agent is that is being excluded and also that the composition, as a whole, remains open to the inclusion of additional elements as evidenced by the use of the transitional phrase "comprising". Applicant's representative suggested potentially amending the claims to recite that the composition "does not include adapalene" or that "the sole agent to treat acne is adapalene". The Examiner indicated that, while it was possible that such amendments may potentially obviate the currently pending art rejections, they may raise the issue of new matter. The Examiner advised Applicant's representative that, should he submit such an amendment to the record, he should explicitly and clearly point to those particular sections of the as-filed specification that he believes provides support for such amendments to the claims. Applicant's representative inquired as to whether the Examiner had searched embodiments of the claimed topical pharmaceutical composition in which adapalene was excluded from the composition (despite the fact that claims definitively excluding this component had not yet been presented in the record). The Examiner replied that a proper search was conducted on the claims as presented and no definitive determination of patentability has made on embodiments not yet presented in the record (in particular, claims that excluded adapalene from the composition as a whole). Applicant's representative indicated that he would consider filing amendments in the case and the Examiner indicated that any amendments submitted to the record would be considered as appropriate.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 14/082,955	**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 --

THE REPLY FILED 21 August 2014 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☒ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection. The current period for reply expires months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANT'S FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☒ They raise the issue of new matter (see NOTE below);
   c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): (a) ☒ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☐ Other: _____.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed: .
    Claim(s) objected to: .
    Claim(s) rejected: 1,3,12,13 and 21-23.
    Claim(s) withdrawn from consideration: 18-20,24-25.

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

Continuation of 3. NOTE: Applicant's request filed August 21, 2014 for entry into AFCP 2.0 is acknowledged, but is denied because the response cannot be reviewed and a search conducted in the limited amount of time authorized for this pilot program. Therefore, the response is being reviewed under pre-pilot practice.

The proposed amendments are not entered because: (i) Applicant proposes to now limit the claims to specifically exclude the component adapalene from the claimed topical pharmaceutical composition, which clearly raises new issues that require further consideration of the presently applied art, as well as a new search to determine the applicability of any additional prior art that would apply to the claims as narrowed by this proposed amendment; (ii) the addition of this new limitation to specifically exclude adapalene from the topical pharmaceutical composition as claimed clearly raises the issue of new matter, as it requires a reassessment of the originally filed disclosure to determine whether there is adequate written support for this newly added limitation, as well as to determine the support for newly added claims 26-30; and (iii) Applicant has added five new claims and cancelled five claims, but the five cancelled claims were not finally rejected (as they were withdrawn from examination as being directed to non-elected subject matter) and, therefore, Applicant has added five new claims without cancelling a corresponding number of finally rejected claims.

Moreover, as the proposed claim amendments clearly raise substantive new issues, they also do not place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

Applicant is entitled only to "cursory" review after-final under pre-pilot practice. MPEP 714.13, part II. "Cursory", or superficial, review does not include substantive consideration of new limitations, particularly when they raise new issues that require further consideration and search. As Applicant's amendments clearly warrant substantive, not cursory, review for the various reasons above, the amendments are not entered into the record.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant requests reconsideration of the present application with regard to the rejections of record in light of the amendments to the claims proposed in the after-final amendment dated August 21, 2014. As the remarks are directed to the obviation of these rejections as a result of the proposed claim amendments, which are not entered into the record for the reasons above, the remarks are not found persuasive.

For these reasons, the claims remain rejected for the reasons of record set forth in the final rejection dated June 11, 2014. Said reasons are herein incorporated by reference, but are not repeated herein so as not to burden the record.

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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	14/082,955	WARNER ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds Draper	1629	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Leslie A. Royds Draper (Primary Exr)*. (3)_____.

(2) *Krishna Banerjee (for Applicant)*. (4)_____.

Date of Interview: *14 August 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☒112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,3,12,13 and 21-23*.

Identification of prior art discussed: *Ahluwalia et al. as used in the 103(a) rejection*.

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(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

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☐ Attachment

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

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

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Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

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- Name of applicant
- Name of examiner
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- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
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1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
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Examiner to Check for Accuracy

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Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant's representative discussed the pending rejection of the claims under 35 U.S.C. 103(a) and indicated that he wished to exclude adapalene from the topical pharmaceutical composition as claimed. The Examiner explained that the phrase "sole active agent" does not definitively exclude this component from the composition as claimed, as it is unclear what the "activity" of the agent is that is being excluded and also that the composition, as a whole, remains open to the inclusion of additional elements as evidenced by the use of the transitional phrase "comprising". Applicant's representative suggested potentially amending the claims to recite that the composition "does not include adapalene" or that "the sole agent to treat acne is adapalene". The Examiner indicated that, while it was possible that such amendments may potentially obviate the currently pending art rejections, they may raise the issue of new matter. The Examiner advised Applicant's representative that, should he submit such an amendment to the record, he should explicitly and clearly point to those particular sections of the as-filed specification that he believes provides support for such amendments to the claims. Applicant's representative inquired as to whether the Examiner had searched embodiments of the claimed topical pharmaceutical composition in which adapalene was excluded from the composition (despite the fact that claims definitively excluding this component had not yet been presented in the record). The Examiner replied that a proper search was conducted on the claims as presented and no definitive determination of patentability has made on embodiments not yet presented in the record (in particular, claims that excluded adapalene from the composition as a whole). Applicant's representative indicated that he would consider filing amendments in the case and the Examiner indicated that any amendments submitted to the record would be considered as appropriate.

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No.	Applicant(s)
	14/082,955	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

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

The amendment document filed on *21 August 2014* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☒ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☒ E. Other: *See Continuation Sheet*.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

_____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **two months** from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

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

Continuation of 4(e) Other:

Newly added claims 26 and 30 are improperly presented with underlining, which fails to comply with 37 CFR 1.121(c). 37 CFR 1.121(c) expressly states that new claims added by amendment must be added in clean version (without any underlining). Note, further, that 37 CFR 1.121(c) contains no provisions for the use of boldfaced type in amended claims. In addition, "Previously canceled" (as used to denote claims 2, 4-11 and 14-17) is not an approved status identifier in accordance with 37 CFR 1.121(c). 37 CFR 1.121(c) indicates that "Canceled" is an approved status identifier to denote a cancelled claim. As such, the amendments are noncompliant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner et al.	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Draper, Leslie A Royds
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

RESPONSE TO FINAL OFFICE ACTION DATED JUNE 11, 2014 - REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE – RESPONSE BEING FILED UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

The following is an amendment and response to the Final Office Action mailed June 11, 2014. Applicant respectfully notes that this is a reply under 37 CFR 1.116 and therefore respectfully requests expedited processing and reply by the Examiner in accordance with the provisions and time periods described in MPEP 714.13(V). Applicant is concurrently filing a Certification and Request for Consideration under the After Final Consideration Pilot Program 2.0.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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	14/082,955	Filing Date	2013-11-18	Docket Number (if applicable)	19107US (AP)	Art Unit	1629
First Named Inventor	Kevin S. Warner			Examiner Name	Leslie A. Royds Draper		

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, 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 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Krishna Banerjee/	Date (YYYY-MM-DD)	2014-09-08
Name	Krishna Banerjee	Registration Number	43317

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.

Electronic Patent Application Fee Transmittal

Application Number:	14082955
Filing Date:	18-Nov-2013
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPLENE COMPOSITIONS AND METHODS FOR USE THEREOF
First Named Inventor/Applicant Name:	Kevin S. Warner
Filer:	Krishna G. Banerjee/Rosemary Kaiwi
Attorney Docket Number:	19107US (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

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($)
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**1200**

Electronic Acknowledgement Receipt

EFS ID:	20078495
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Krishna G. Banerjee/Rosemary Kaiwi
Filer Authorized By:	Krishna G. Banerjee
Attorney Docket Number:	19107US (AP)
Receipt Date:	08-SEP-2014
Filing Date:	18-NOV-2013
Time Stamp:	17:59:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1200
RAM confirmation Number	5057
Deposit Account	010885
Authorized User	

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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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		19107_Resp_to_Notice_of_Noncompl_Amend_090814.pdf	122803 ca43568d1cfbd3c31d7843770ab2383535dd2d7a	yes	10

Multipart Description/PDF files in .zip description

Document Description	Start	End
Response After Final Action	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	10

Warnings:

Information:

2	Request for Continued Examination (RCE)	19107US_RCE_Transmittal.pdf	797991 ed0ca44a93058b2cc47e207e719aeb9a04094d24	no	3

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	30729 10a960be7e97025dd064a6c3500d5fc03d368ff2	no	2

Warnings:

Information:

Total Files Size (in bytes):	951523

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner et al.	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Draper, Leslie A Royds
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

AMENDMENTS & RESPONSE TO NOTICE OF NON-COMPLIANT AMENDMENT (37 CFR 1.121) OF AUGUST 29, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

The following is response to the Notice of Non-Compliant Amendment (37 CFR 1.121) dated August 29, 2014. On August 21, 2014, Applicant had filed an amendment and response to the final office action of June, 11, 2014, for which the applicant received the above Notice of Non-Compliant Amendment. The present amendment and response is identical to the response filed on August 21, 2014, except that it addresses the aforementioned Notice of Notice of Non-Compliant Amendment.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Amendments to the Claims

The following claims replace all prior claims presented in this application.

1. (Currently amended) A topical pharmaceutical composition comprising:

about 7.0% w/w to about 8.0% w/w dapsone ~~as the sole active agent~~;

about 25% w/w to about 35% 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.

2. (Canceled)

3. (Previously presented) The composition of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

Claims 4-11. (Canceled)

12. (Original) The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

13. (Original) The composition of claim 1, further comprising methyl paraben.

Claims 14-20. (Canceled)

21. (Previously presented) The composition of claim 1, wherein the dapsone is present in the composition at a concentration of about 7.5% w/w.

22. (Currently amended) A topical pharmaceutical composition comprising:

about 7.5% w/w dapsone ~~as the sole active agent~~;

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 composition does not comprise adapalene.

23. (Previously presented) The composition of claim 22, further comprising methyl paraben.

Claims 24-25. (Canceled)

26. (New) A topical pharmaceutical composition for the treatment of acne, comprising:

about 7.0% w/w to about 8.0% w/w dapsone;

about 25% w/w to about 35% 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 dapsone is the sole active agent for the treatment of acne in the composition.

27. (New) The composition of claim 26, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

28. (New) The composition of claim 26, further comprising methyl paraben.

29. (New) The composition of claim 26, wherein the dapsone is present in the composition at a concentration of about 7.5% w/w.

30. (New) A topical pharmaceutical composition for the treatment of acne, 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 dapsone is the sole active agent for the treatment of acne in the composition.

REMARKS/ARGUMENTS

The undersigned attorney thanks the Examiner for the courtesy extended to him to discuss this case through a phone interview on August 14, 2014.

Claims 1-3, 12, 13, and 18-25 were pending in the application. In the present Amendment, Applicant has amended claims 1 and 22; canceled claims 18-20, and 24-25; and added new claims 26-29. All of the claim amendments and new claims are fully supported by the specification as filed, and no new matter has been added.

Support for the recitation "wherein the composition does not comprise adapalene" in amended claims 1 and 22, and for the recitation "for the treatment of acne" and "wherein the dapsone is the sole active agent for the treatment of acne in the composition" in new claims 26 and 30 can be found for example in Table 1 (page 15 of the specification, wherein only dapsone and no adapalene is used in the formulation); in paragraph [009], pages 2-3 (referring to dapsone and dapsone/adapalene compositions useful for treating a variety of dermatological condition, including acne); paragraph [006], page 2 of the specification (referring to a need for compositions and methods used in the treatment of acne); paragraph [008], page 2 of the specification (referring to the use of dapsone as an anti-inflammatory agent, and to its use to treat *acne vulgaris*); paragraph [004], pages 1-2 of the specification (referring to "active agent known to have anti-acne activity").

Claim Rejections under 35 U.S.C. § 112

On pages 2-3 of the Action, claims 1, 3, 12-13 and 21-23 stand rejected under 35 U.S.C. 112 (b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly 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.

The Examiner refers to the phrase "the sole active agent", and asserts that this phrase renders the term indefinite because it is unclear what "activity" of other agents is eliminated by phrase. The Examiner also asserts that there is insufficient antecedent basis for this term.

The phrase "sole active agent' is no longer used in currently amended claims 1 and 22; according this rejection is moot with respect to these claims, and claims

dependent thereon, viz., claims 12-13, 21, and 23. In so far as this rejection is applied to new claims 26-30, Applicant traverses this rejection.

Claims 26 and 30 recite that "dapsone is the sole active agent for the treatment of acne in the composition". Thus the "activity" here clearly refers to the anti-acne activity of dapsone. The claim language also makes it clear, that other than dapsone, there is no other ingredient in the claimed composition that has "anti-acne" activity. The phrase "active agent" has the same meaning as "active ingredient (AI)"/ "active pharmaceutical ingredient (API)", and in conjunction with the phrase "for the treatment of acne" leaves no room for ambiguity that the "activity" here refers to the "anti-acne" activity. Applicant also does not find any lack of antecedent basis in claims 26-30.

Accordingly, Applicant respectfully requests the Examiner to withdraw the rejection.

Rejections under 35 U.S.C. § 103

On pages 3-7 of the Action, claims 1, 3, 12-13 and 21-23 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Ahluwalia et al. (WO 2011/014627 A1; February 2011; hereinafter "Ahluwalia") in view of Hani et al., (WO2010/105052 A1; hereinafter "Hani"), citing to Garrett (WO 2009/108147 A1; 2009), Villa (U.S. Patent 7,531,694; 2009), and Dreno (U.S. Patent Application Publication No. 2010/0130613; 2010) to show facts,.

The Examiner cites Ahluwalia for allegedly teaching compositions comprising dapsone and adapalene for the treatment of acne and other dermatological conditions (referring to abstract). The Examiner refers to Ahluwalia teaching that dapsone/adapalene compositions preferably contain, *inter alia*, 0.5-10% w/w dapsone and 0.1-0.3% w/w adapalene, as well as 1-50% w/w diethylene glycol monoethyl ether and 1-8% w/w hydroxyethyl cellulose as a thickener (referring to Table 1, p.8).

The Examiner cites Garrett for allegedly teaching that TRANSCUTOL is synonymous with DGME, which is diethylene glycol monoethyl ether (referring to Garrett, p. 14, l. 5-6).

The Examiner cites Villa for allegedly teaching that dapsone is an antibacterial agent (col. 1, l. 10-16), and Dreno for allegedly teaching that adapalene is a retinoid that

affects cell differentiation and exerts an anti-inflammatory effect (referring to p. 1, para. [0023]). The Examiner asserts that as adapalene does not possess the same therapeutic activity as dapsone, it is therefore, not patentably excluded from the instant claims as being another "active agent" with the same activity as dapsone.

The Examiner cites Hani for allegedly teaching that acrylamide/sodium acryloyldimethyltaurate copolymer is a thickener or viscosity increasing agent suitable for use in topical personal care compositions (p. 24-28, para [0018]; abstract).

The Examiner asserts that a person of ordinary skill in the art before the effective date of the claimed invention would have had a reasonable expectation of success in substituting the hydroxyethyl cellulose thickener of the dapsone formulation described in Ahluwalia as being advantageously incorporated in an amount of 1-8% w/w, particularly 2% w/w or 4% w/w, 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 Ahluwalia and Hani.

The Examiner concludes by asserting that Ahluwalia clearly teaches the use of every component recited the present composition in amounts that clearly meet or encompass the ranges specifically recited in the present claims, and that a person of ordinary skill in the art before the effective date of the claimed invention would have had a reasonable expectation of success in varying the amount of the components of the composition as described in Ahluwalia within the disclosed ranges therein.

Applicant respectfully disagrees with the Examiner's position and traverses this rejection. Applicant contends that the cited references alone or in combination do not teach or suggest all the claim limitations.

In *Graham* v. *John Deere Co. of Kansas City,* 383 U.S. 1 (1966), the court set out a framework for applying the statutory language of § 103, language itself based on the logic of the earlier decision in *Hotchkiss v. Greenwood*, 11 How. 248 (1851), and its progeny. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). It is an objective analysis.

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the

obviousness or nonobviousness of the subject matter is determined. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

It is well settled that *Graham v. John Deere Co.* is to be followed in the consideration and determination of obviousness under 35 U.S.C. § 103. In doing so, four factual inquiries are made:

(1) Determining the scope and contents of the prior art;

(2) Ascertaining the differences between the prior art and the claims in issue;

(3) Resolving the level of ordinary skill in the pertinent art; and

(4) Evaluating relevant evidence of secondary considerations.

When applying 35 U.S.C. § 103, the following basic considerations of law must be adhered to: (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention, and (4) reasonable expectation of success is the standard with which obviousness is determined. MPEP 2141-45, 8th ed., 2007 (*Hodosh* v. *Block Drug Co.,* 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986), *cert. denied,* 479 U.S. 827 (1986)).

To reach a proper determination under 35 U.S.C. § 103, the Examiner must view all factual information and then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. *Gillette Co.* v. *S.C. Johnson & Son, Inc.,* 919 F.2d 720, 724 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 796 F.2d 443, 449 (Fed. Cir. 1986), *cert. denied,* 484 U.S. 823 (1987). The law is quite clear that all of the evidence must be considered, not simply that which supports the Examiner's position.

In particular, to avoid hindsight analysis, a court "flexibly seeks evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination." *Rolls-Royce, PLC. v. United Techs. Corp.*, 2010 U.S. App. LEXIS 9201 at *27-*28 (Fed. Cir. May 5, 2010); *see e.g., Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1363-68 (Fed. Cir. 2008).

To establish *a prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *Id.*

As instructed by the Supreme Court in *KSR*, an invention may be obvious if it would have been obvious to a person of ordinary skill to try a particular course of conduct. In particular, the Supreme Court stated that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue known options within his or her technical grasp. *KSR*, 550 U.S. at 420. Consistent with the Supreme Court's instruction, the Federal Circuit has described at least two classes where this reasoning does not apply. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009).

First, an invention would not be obvious or obvious to try when the ordinary artisan would have to try all possibilities in a field without any direction by the prior art. *Id.* "When 'what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful' and invention would not have been obvious." *Id.* (quoting *O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

This reasoning is consistent with *KSR*'s requirement that there be a "finite number of identified….solutions" and the number of options to be "small or easily traversed." *Id.*[1] Second, an invention is not obvious or obvious to try where the prior art

[1] For example, in *In re Omeprazole patent Litig. v. Apotex Corp.,* 536 F.3d 1361 (Fed. Cir. 2008), the Federal Circuit gave considerable weight to the fact that even if one ordinarily skilled in the art would

does not guide the ordinary artisan toward a particular solution. *Id*. This reasoning is consistent with *KSR*'s requirement that the solutions be predictable, and not otherwise an exploration of a general approach that seemed to be a promising field of experimentation. *Id*. The Federal Circuit has commented that "to the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *P&G v. Teva Pharms. USA, Inc.,* 566 F.3d 989, 996 (Fed. Cir. 2009) (quoting *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1353, 1359 (Fed. Cir. 2008)).

Present claims 1 and 22 clearly exclude adapalene from the scope of the claimed composition. Ahluwalia does not disclose or suggest a composition where adapalene is not an ingredient of the composition. Therefore , with respect to these claims, Ahluwalia, as the primary reference, alone or in combination with Hani, Garrett, Villa and Dreno, does not render obviously the composition of these claims.

With respect to new claims 26 and 30, again the cited references alone, or in combination do not teach or suggest the compositions claimed therein, wherein dapsone is the sole active agent for the treatment of acne in the composition. With regard to the Examiner's comments that the therapeutic activity of dapsone (referred to as an antibacterial agent in Villa) and adapalene (referred to as affecting cell differentiation and having an anti-inflammatory effect in Dreno) are different, Applicant notes that notwithstanding such effects or regardless of such effects, it is clear to one of ordinary skill in the art that both adapalene and dapsone are anti-acne agents, i.e., they are active pharamaceutical ingredients suitable for the treatment of acne. As present claims 26 and 30 exclude any anti-acne agent other than dapsone, they are not rendered obvious in view of the cited references.

Applicants respectfully submit that the presently claimed compositions are not obvious in view of the cited references, and respectfully requests the Examiner to withdraw the present rejection.

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have recognized a particular problem, such a person would have been faced with multiple paths to solving the problem and would have been more likely to have chosen a solution different from the claimed invention in light of the known characteristics of the subject matter. In light of this, the Federal Circuit upheld the finding of nonobviousness of the district court.

CONCLUSION

The above is believed to be a complete response to each and every ground of rejection as set for the in the Action dated June 11, 2014. The Examiner is respectfully invited to call the undersigned attorney to discuss any aspect of the present response to expedite prosecution and allowance of this case. If any fees are deemed due in connection with the filing of this Amendment, the Office is authorized to charge said fees Deposit Account 01-0885 or to credit any overpayment.

Respectfully submitted,

Dated: September 8, 2014

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/082,955	Filing Date 11/18/2013	☐ 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 **09/08/2014**

	(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))	* 4	Minus	***4	= 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
/YOLANDA CHADWICK/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 12/01/2014

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EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
12/01/2014	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. 14/082,955	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 *08 September 2014*.

☐ 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) *1,3,12,13,21-23,26-30* 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) *1,3,12,13,21-23 and 26-30* is/are rejected.

8)☐ Claim(s) _____ 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, 3, 12-13, 21-23 and 26-30 are presented for examination.

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 8, 2014 has been entered.

Claims 1, 3, 12-13, 21-23 and 26-30 are pending and under examination. Claims 26-30 are newly added. Claims 18-20 and 24-25 are cancelled. Claims 1 and 22 are amended.

Applicant's arguments, filed September 8, 2014, 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 Claim Listing Filed September 8, 2014

Applicant's claim listing filed as part of the after-final amendment submitted August 21, 2014 was non-compliant as detailed in the Notice of Non-Compliant Amendment mailed August 29, 2014 with the Advisory Action of the same date. Applicant's presentation of claims 2, 4-11 and 14-17 with the status identifier of "Previously Canceled" in the claim listing of August 21, 2014 was determined to be improper, as was the presentation of new claims 26 and 30 with bolded typeface and underlining (as 37 C.F.R. 1.121(c) expressly states that new claims added by amendment must be added in clean version without any underlining). Applicant now presents an updated claim listing with the submission of September 8, 2014, fixing these deficiencies. However, Applicant previously sought addition of new claims 26-30 in the after-final amendment submitted August 21, 2014, but the claims were not entered into the record as indicated in the Advisory Action dated August 29, 2014. As a result, claims 26-30 should be provided with

the status identifier of "Not Entered", and any claims sought to be added should be numbered with the next consecutive number (i.e., starting at 31). See 37 C.F.R. 1.121(c). In the interest of compact prosecution, the claim listing of September 8, 2014 will be entered and treated on the merits solely because the discrepancy relates to the numbering of the claims and not the actual subject matter under examination.

Applicant is notified, however, that this error must be rectified in any future submissions of claim listings in the instant application. Submission of claims that do not explicitly comply with the requirements of 37 C.F.R. 1.121(c) will not be entered into the record and notice to this effect will be mailed to Applicant. Repeated submissions of non-compliant claim amendments may delay substantive prosecution on the merits and may be considered non-*bona fide* attempts at reply. Applicant is strenuously urged to review the requirements of 37 C.F.R. 1.121(c) *prior* to filing any claim listings in any future submissions to ensure full compliance with the stipulations of this rule.

Claim Rejections - 35 USC § 112(b) (New Grounds of Rejection)

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 26-30 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.

In claims 26 and 30, there is insufficient antecedent basis for the term “the sole active agent”. Clarification is required.

As claims 27-29 depend from claim 26 and do not clarify this point of confusion, they must also be rejected on this same ground.

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

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

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, 3, 12-13, 21-23 and 26-30 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 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" (claims 1 and 26), particularly about 4% w/w (claims 12, 22 and 30) or (2) the exact claimed amount of DGME (i.e., “about 30% w/w”; claims 3, 22, 27 and 30) or the exact claimed range of dapsone (i.e., "about 7.0% w/w to about 8.0% w/w or "about 7.5% w/w"; claims 1, 21-22, 26 and 29-30).

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 ranges of:

(i) "about 7.0% w/w to about 8.0% w/w" dapsone (claims 1 and 26) or "about 7.5% w/w" dapsone (claims 21-22 and 29-30);

(ii) "about 30% w/w" DGME (claims 3, 22, 27 and 30); and

(iii) "about 2% w/w to about 6% w/w" polymeric thickener (claims 1 and 26), particularly "about 4% w/w" (claims 12, 22 and 30).

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, 12, 22, 26 and 30).

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.

Claims 1, 3, 12-13, 21-23 and 26-30 are rejected under 35 U.S.C. 103 as being unpatentable over Lathrop et al. (U.S. Patent Application Publication No. 2006/0204526; 2006) in view of Garrett (WO 2009/108147 A1; 2009), further in view of Hani et al. (WO 2010/105052 A1; 2010), citing to Lubrizol ("Viscosity of CARBOPOL Polymers in Aqueous Systems", August 2010; Online) to show a fact.

Lathrop et al. teaches topical emulsive compositions of dapsone (abstract). Lathrop et al. teaches that dapsone may range from preferably about 0.005-30% w/w, about 0.1-25% w/w, about 0.1-15% w/w,

about 0.1-10% w/w, about 0.2-8% w/w and about 0.5-5% w/w of the composition, with amounts of 1.0% w/w, 2.0% w/w, 5.0% w/w and 7.5% w/w being especially preferred (p.2, para.[0014]). Lathrop et al. teaches the following exemplary compositions:

(i) Ex.2 (p.7, para.[0093]), which comprises 3% w/w dapsone; 0.25% w/w CARBOPOL 980; 15% w/w ethoxydiglycol (i.e., diethylene glycol monoethyl ether; see, e.g., p.5, para.[0056]); 0.2% w/w methyl paraben; 0.25% w/w sodium hydroxide solution; and purified water; and

(ii) Ex.8 (p.9, para.[0134]), which comprises 3% w/w dapsone; 15% w/w propylene glycol; 15% w/w ethoxydiglycol; 0.4% w/w CARBOPOL 980; 0.15% w/w methyl paraben; triethanolamine; and purified water.

Lubrizol teaches that CARBOPOL 980 is a polymeric thickener (Table 1B; p.2).

Lathrop et al. differs from the instant claims insofar as it does not explicitly teach (1) acrylamide/sodium acryloyldimethyl taurate copolymer in an amount of "about 2% to about 6% w/w" (claims 1 and 26), particularly about 4% w/w (claims 12, 22 and 30) or (2) the exact claimed range of DGME (i.e., “about 25% to about 35% w/w" or “about 30% w/w”; claims 1, 3, 22, 26-27 and 30) or the exact claimed range of dapsone (i.e., "about 7.0% w/w to about 8.0% w/w or "about 7.5% w/w"; claims 1, 21-22, 26 and 29-30).

Garrett teaches dapsone compositions with a pharmaceutically acceptable carrier for topical delivery of dapsone (p.12, l.1-2), wherein the composition comprises between 0.5-10% w/w dapsone (p.19, l.24-25).Garrett teaches that the topical composition preferably includes a thickening agent or thickener, 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 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).

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 CARBOPOL 980 polymeric thickener of the dapsone formulation described in Lathrop et al. 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. The substitution, therefore, of one for the other would have been *prima facie* obvious before the effective filing date of the claimed invention because CARBOPOL 980 and acrylamide/sodium acryloyldimethyl taurate copolymer were 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, the teachings in Lathrop et al. clearly suggest suitable amounts of dapsone for use in the disclosed topical formulation that clearly circumscribe and/or suggest the amounts instantly claimed. See, e.g., Lathrop et al. at p.2, para.[0014], which discloses the use of 0.005-30% w/w, about 0.1-25% w/w, about 0.1-15% w/w, about 0.1-10% w/w, about 0.2-8% w/w and about 0.5-5% w/w of the composition, with amounts of 1.0% w/w, 2.0% w/w, 5.0% w/w and 7.5% w/w being especially preferred. Such ranges clearly encompass Applicant's instantly claimed ranges of dapsone from "about 7.0% w/w to about 8.0% w/w" (claims 1 and 26) or "about 7.5% w/w" (claims 22 and 29-30). Thus, Lathrop et al. clearly suggests the incorporation of dapsone in amounts that clearly meet or encompass the ranges specifically recited in the present claims. Note that, where ranges overlap or lie inside ranges disclosed by the prior art, a *prima facie* case of obviousness exists. MPEP §2144.05.

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 amount of dapsone within the suggested ranges therein because Lathrop et al. teaches that dapsone may be employed in varying amounts within the described parameters, while retaining the therapeutic functionality of the composition. The selection of the optimal amount of dapsone would have been a matter of routine optimization on the part of the artisan of ordinary skill, said artisan recognizing that dapsone may be varied within the broader ranges described in Lathrop et al. while still preserving the therapeutic properties of the composition. Moreover, the fact that the claimed amounts overlap and fall within those suggested by the prior art is evidence of *prima facie* obviousness. See, again, MPEP §2144.05.

In addition, the 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 amount of polymeric thickener to be employed in the dapsone formulation of Lathrop et al. to be "about 4.0% w/w" as instantly claimed or the amount of DGME to be “about 25% to about 35% w/w” (particularly "about 30% w/w") because Garrett suggests the incorporation of from 0.2-4% w/w polymeric thickener and from about 25-35% w/w glycol ether into topical formulations of 0.5-10% w/w dapsone (which circumscribes the amount of dapsone employed in the topical formulations of Lathrop et al.). The skilled artisan would have found it *prima facie* obvious to modify the amount of the polymeric thickener and/or solvent to be within the ranges suggested by Garrett depending upon the desired viscosity of the formulation and the degree of dissolution of dapsone desired in the mixture. The selection of the optimal amount of polymeric thickener and/or glycol ether from the ranges suggested by the prior art would have been a matter of routine optimization on the part of the artisan of ordinary skill, said artisan recognizing that the amounts of polymeric thickener and/or glycol ether may be varied within those ranges suggested by Garrett to be suitable for topical formulations of dapsone comprising similar amounts by weight of dapsone while still preserving the therapeutic properties of the composition.

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.

Response to Applicant's Arguments

Applicant traverses the previously applied rejections and requests withdrawal of the previously applied rejections in view of the remarks and amendments to the claims.

Applicant's traversal and amendments have been fully and carefully considered and the previously applied rejections have been withdrawn. However, upon reconsideration of the claimed subject matter, new grounds of rejection are set forth *infra*.

For these reasons *supra*, rejection of claims 1, 3, 12-13, 21-23 and 26-30 is proper.

Conclusion

Rejection of claims 1, 3, 12-13, 21-23 and 26-30 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.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application in order to assist the examiner with double patenting analysis in the application.

The examiner may not initiate communications via electronic mail unless and until applicants authorize such communications in writing within the official record of the patent application. See M.P.E.P. § 502.03, part II. A sample authorization is available at § 502.03, part II.

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 24, 2014

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	6642	dapson$2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:37
L2	22525	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:38
L3	236497	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:39
L4	26452	(methyl adj2 paraben)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:39
L5	4	1 and 2 and 3 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:39
L6	2	"20060204526".did.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:46
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L9	3	"20100029781".did.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 14:52
L10	24422	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) transcutol$	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 15:12
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L12	3	11 not 7	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/11/24 15:13

11/24/2014 3:13:45 PM
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                D L1

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L5          4098 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W)GLYCOL(W)MONOETHYL?
                (W)ETHER?) OR (ETHOXY(W)DIGLYCOL?) OR TRANSCUTOL?
L6         91644 SEA ABB=ON  PLU=ON  ACRYLAMID? OR (SODIUM(W)ACRYLOYL(W)DIMETHYL
                (W)TAURAT?) OR (ACRYLAMID?(2A)SODIUM(2A)ACRYLOYL(2A)DIMETHYL(2A
                )TAURAT?)
L7         10425 SEA ABB=ON  PLU=ON  (METHYL(W)PARABEN?) OR METHYLPARABEN?
L8             1 SEA ABB=ON  PLU=ON  L4 AND L5 AND L6 AND L7
                D L8 1 IBIB ED ABS
L9             2 SEA ABB=ON  PLU=ON  L4 AND L5 AND L7 AND (WATER?)
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L17        20675 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
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                 DIMETHYL(2A) TAURAT?)
L19        47312 SEA ABB=ON  PLU=ON  (METHYL(W) PARABEN?) OR METHYLPARABEN?
L20            6 SEA ABB=ON  PLU=ON  L16 AND L17 AND L18 AND L19
L21            6 DUP REM L20 (0 DUPLICATES REMOVED)
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     FILE HOME

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     Property values tagged with IC are from the ZIC/VINITI data file
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     STRUCTURE FILE UPDATES:   23 NOV 2014  HIGHEST RN 1637213-20-7
     DICTIONARY FILE UPDATES:  23 NOV 2014  HIGHEST RN 1637213-20-7

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     FILE LAST UPDATED: 23 Nov 2014 (20141123/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Nov 2014
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Sep 2014

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FILE LAST UPDATED: 24 Nov 2014 (20141124/UP). FILE COVERS 1946 TO DATE.

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In preparation for the annual MEDLINE reload for 2015, please note the following:

- The NLM is not supplying MEDLINE updates for Thursday, November 20 through Sunday, November 23.

- From Monday, November 24 through approximately Wednesday, December 17, MEDLINE updates will consist only of "In-process" and "In-Data-Review" documents. These documents lack MeSH Indexing.

- Normal updating is expected to resume in mid-December.

Effective June 2014, MEDLINE is now updated daily - seven days per week. Alerts running on a frequency of Every Update will now be delivered seven times per week. See NEWS for further information.

The 2014 MEDLINE reload was completed on January 26, 2014.
See HELP RLOAD for details on new search capabilities introduced with the reload.

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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: 19 November 2014 (20141119/ED)

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FILE EMBASE
FILE COVERS: Embase-originated material 1947 to 24 Nov 2014 (20141124/ED)
Unique MEDLINE content 1948 to present
Emtree thesaurus last updated September 2014

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Effective July 28, 2013, 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. See NEWS for

details.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 20 Nov 2014 (20141120/PD)
FILE LAST UPDATED: 20 Nov 2014 (20141120/ED)
HIGHEST GRANTED PATENT NUMBER: US8893311
HIGHEST APPLICATION PUBLICATION NUMBER: US20140344993
CA INDEXING IS CURRENT THROUGH 16 Nov 2014 (20141116/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Nov 2014 (20141120/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

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FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 20 Nov 2014 (20141120/PD)
FILE LAST UPDATED: 20 Nov 2014 (20141120/ED)
HIGHEST GRANTED PATENT NUMBER: US8893311
HIGHEST APPLICATION PUBLICATION NUMBER: US20140345027
CA INDEXING IS CURRENT THROUGH 16 Nov 2014 (20141116/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 20 Nov 2014 (20141120/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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)	03/18/14	LARD
WEST Search (See Attached Search History)	03/18/14	LARD
Updated Inventor Search (PALM Database, eDAN)	06/05/14	LARD
Updated WEST Search (See Attached Search History)	06/05/14	LARD
Updated Inventor Search (PALM Database, eDAN)	11/24/14	LARD
EAST Search (See Attached Search History)	11/24/14	LARD
STN Search (See Attached Search History)	11/24/14	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	24 November 2014

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

AMENDMENTS & RESPONSE TO OFFICE ACTION OF DECEMBER 1, 2014

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

Please enter the following amendments and remarks in response to the Non-Final Office Action dated December 1, 2014.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

The following listing of claims replaces all prior versions presented in this application.

1. (Currently Amended) A topical pharmaceutical composition comprising:

about 7.5% ~~7.0% w/w to about 8.0%~~ w/w dapsone;

about 30[[25]]% w/w to about 40[[35]]% 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.

2. (Canceled).

3. (Previously Presented) The composition of claim 1, wherein the diethylene glycol monoethyl ether is present at a concentration of about 30% w/w.

4. - 11. (Canceled).

12. (Original) The composition of claim 1, wherein the polymeric viscosity builder is present at a concentration of about 4% w/w.

13. (Original) The composition of claim 1, further comprising methyl paraben.

14. - 21. (Canceled).

22. (Previously Presented) 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 composition does not comprise adapalene.

23. (Previously Presented) The composition of claim 22, further comprising methyl paraben.

24.- 30. (Canceled).

REMARKS/ARGUMENTS

Claims 1, 3, 12, 13, 21-23 and 26-30 are presently pending and under consideration. Claims 26-30 are hereby canceled. Claim 1 is hereby amended to incorporate the recitation of claim 21, which is canceled. Claim 1 is also amended to recite a range of about 30% w/w to about 40% w/w diethylene glycol monoethyl ether as recited in paragraph [028] of the specification.

These amendments render moot the objection to the claim listing of September 8, 2014. No new matter is added by the amendments.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 26-30 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. This rejection is moot in view of the above amendment.

Rejections under 35 U.S.C. § 103

Garrett in view of Hani

Claims 1, 3, 12-13, 21-23 and 26-30 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Garrett (WO 2009/108147 A1) in view of Hani *et al.*, (WO 2010/105052 A1). Specifically, the Examiner alleges that Garrett teaches dapsone compositions prepared for topical delivery, including in compositions comprising 5% dapsone and excipients which overlap in part with the excipients of the claimed compositions. *See* Office Action, pages 4-5. The Examiner further alleges that what is not taught by Garrett is taught by Hani – that "acrylamide/sodium acryloyldimethyl taurate copolymer is a thickener or viscosity enhancing agent suitable for use in topical personal care compositions." *Id.* at 5. Applicant respectfully disagrees with the grounds for rejection.

First, Garrett teaches (as admitted by the Patent Office) 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 law of obviousness was discussed in Applicant's previous response. Applicant 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, 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.

Lathrop in view of Garrett and Hani

Claims 1, 3, 12-13, 21-23 and 26-30 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Lathrop *et al.* (US 2006/0204526) in view of Garrett and Hani, further in view of the Lubrizol product description of Carbopol® 980. Applicant respectfully disagrees with the grounds for rejection.

Garrett and Hani are discussed above. Lathrop teaches emulsive compositions of dapsone, wherein 7.5% is one of four preferred percentages. Lathrop does not teach

or suggest the use of Sepineo™ P 600 as a thickening agent, compositions comprising dapsone/Sepineo™ P 600 compositions, nor such compositions at the specific amounts recited in the instant claims. In addition, Lathrop requires an "oil phase component" in its compositions. Page 1, [0009]. Indeed, it is a distinguishing element from the prior art discussed by Lathrop. *Id.* at [0007]. An oil component is not required in the compositions of the instant claims. Lathrop therefore adds nothing to the deficiencies of Garrett and Hani, in that it does not teach or provide any suggestion of the specific combination of elements discussed above.

The Patent Office points to Examples 2 and 8 of Lathrop at page 8 of the Office Action, but there is no explanation as to how these examples would lead one of ordinary skill in the art to the claimed invention. Indeed, these compositions recite only 3% w/w dapsone, Carbopol 980 instead of Sepineo™ P 600, and further comprise many other additional ingredients not listed in the Office Action (*e.g.*, white petrolatum, isopropyl palpitate, Emulium Delta®) which would lead one of ordinary skill ***away from*** the composition of the instant claims. Again, the Patent Office's reliance on *KSR* at page 9 of the Office Action is misguided for the same reasons discussed above. There simply is not enough evidence presented in the Office Action to proper state a *prima facie* case of obviousness based on the cited references.

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 Applicant has 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 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. Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

In conclusion, the above amendments and remarks are believed to be a complete response to each and every ground of rejection as set for the in the pending Office Action. The Examiner is respectfully invited to call the undersigned attorney at 714-246-2276 to discuss any aspect of the present response to expedite prosecution and allowance of this case. If any fees are deemed due in connection with the filing of this Amendment, the Office is authorized to charge said fees Deposit Account 01-0885 or to credit any overpayment.

Respectfully submitted,

Dated: February 2, 2015

/Mark D. Kafka/
Mark D. Kafka
Registration No. 59,569
Attorney for Applicants

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.

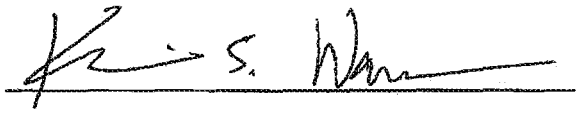
9. In additional experiments under my supervision, a dapsone particle size assessment revealed that formulations thickened with Sepineo P 600 provided a smaller dapsone particle size as compared to Carbopol 980. The compositions of the formulations evaluated for particle size are outlined in Table 1 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:	21376512
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	Mark Kafka/Maria Stein
Filer Authorized By:	Mark Kafka
Attorney Docket Number:	19107US (AP)
Receipt Date:	02-FEB-2015
Filing Date:	18-NOV-2013
Time Stamp:	18:17:28
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		19107-Resp-NFOA-02022015a.pdf	844550 67ca46d836ea29da9cbb0e9636c6774b0c57088e	yes	13

	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	8
	Affidavit-traversing rejectns or objectns rule 132	9	13
Warnings:			
Information:			
	Total Files Size (in bytes):	844550	

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
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NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 03/19/2015

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

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 03/19/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

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	06/19/2015

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**
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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 03/19/2015
ALLERGAN, INC.
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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.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

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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	06/19/2015

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. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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51957 7590 03/19/2015

ALLERGAN, INC.
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IRVINE, CA 92612-1599

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 03/19/2015

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. 14/082,955	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 amendment papers filed February 2, 2015*.
   ☐ 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 *1,3,12,13,22 and 23*. 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 11/18/13 are accepted*.

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/136 (See Attached Text Search Within this Subclass)	03/09/15	LARD
A61K 9/0014 (See Attached Text Search Within this Subclass)	03/09/15	LARD

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	646 (See Attached Text Search Within this Subclass)	03/09/15	LARD

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search (PALM Database, eDAN)	03/18/14	LARD
WEST Search (See Attached Search History)	03/18/14	LARD
Updated Inventor Search (PALM Database, eDAN)	06/05/14	LARD
Updated WEST Search (See Attached Search History)	06/05/14	LARD
Updated Inventor Search (PALM Database, eDAN)	11/24/14	LARD
EAST Search (See Attached Search History)	11/24/14	LARD
STN Search (See Attached Search History)	11/24/14	LARD
Updated Inventor Search (PALM Database, eDAN)	03/09/15	LARD
Updated EAST Search (See Attached Search History)	03/09/15	LARD
Updated STN Search (See Attached Search History)	03/09/15	LARD

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/136 (See Attached Text Search within this Subclass)	03/09/15	LARD

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	09 March 2015

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
A61K	9/0014 (See Attached Text Search within this Subclass)	03/09/15	LARD
514	646 (See Attached Text Search within this Subclass)	03/09/15	LARD

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	09 March 2015

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	8752	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:09
L2	0	"4-[(4-aminobenzene)sulfonyl]aniline" "4-[(4-aminobenzene)sulphonyl]aniline"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:10
L3	23107	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:11
L4	241209	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:12
L5	8752	1 or 2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:12
L6	16	5 and 3 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:12
L7	16	6 and (water (purified adj water) aqueous)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:12
L8	24765	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:16
L9	16	5 and 8 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:16
L10	0	9 not 6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:16

L11	1873	(514/646).ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:16
L12	64	11 and (dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:17
L13	2	12 and 8 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:17
L14	2813	(A61K31/136).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:17
L15	113	14 and (dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:17
L16	43979	(A61K9/0014).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:18
L17	17	16 and 15	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:18
L18	1	17 and (4 and 8)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:18
L19	16	17 not 9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:18
L20	1	17 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/03/09 12:22

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L21	1333	(514/646).ccls.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:23

L23	7181	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:23
L24	631	(dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:23
L25	1592	("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:24
L26	26709	((acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:24
L27	31	21 and 24	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:24
L28	1	27 and (25 and 26)	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:24
L29	578	(A61K31/136).CPC.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25
L30	8222	(A61K9/0014).CPC.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25
L31	23	29 and 24	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25
L32	1	31 and (25 and 26)	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25
L33	11	29 and 30	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25
L34	5	33 and 24	US-PGPUB; USPAT; UPAD	OR	OFF	2015/03/09 12:25

3/9/2015 12:29:17 PM
C:\Users\lroyds\Documents\EAST\Workspaces\14082955.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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
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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 (Assistant Examiner)	(Date)	**Total Claims Allowed:** 6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629 (Primary Examiner)	09 Mar 15 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No. 20150309

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	WARNER ET AL.
	Examiner	**Art Unit**
	Leslie A. Royds Draper	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
514	646	A	6	1	K	31 / 136 (2006.01.01)	A	6	1	K	31 / 192 (2006.01.01)

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	09 Mar 15	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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		17												
	2		18												
2	3		19												
	4		20												
	5		21												
	6	5	22												
	7	6	23												
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	10		26												
	11		27												
3	12		28												
4	13		29												
	14		30												
	15														
	16														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629 (Primary Examiner)	09 Mar 15 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

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

BIB DATA SHEET

CONFIRMATION NO. 1222

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/082,955	11/18/2013	514	1629	19107US (AP)

APPLICANTS

ALLERGAN, INC., IRVINE, CA, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

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

Drawings filed 11/18/13 are accepted.

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

This appln claims benefit of 61/728,403 11/20/2012
and claims benefit of 61/770,768 02/28/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/02/2013

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	20	1

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		
2320	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

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=> d his full

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L1             1 SEA ABB=ON  PLU=ON  DAPSONE/CN

     FILE 'CAPLUS' ENTERED AT 12:37:59 ON 09 MAR 2015

     FILE 'REGISTRY' ENTERED AT 12:38:52 ON 09 MAR 2015
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L2              SEL PLU=ON  L1 1- CHEM :      65 TERMS
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L3         17699 SEA ABB=ON  PLU=ON  L2
L4         17732 SEA ABB=ON  PLU=ON  L3 OR DAPSON? OR (DIAMINO(W)DIPHENYL(W)(SUL
                 FON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULFONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULPHONYL]ANILINE")
L5          4236 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W)GLYCOL(W)MONOETHYL?
                 (W)ETHER?) OR (ETHOXY(W)DIGLYCOL?) OR TRANSCUTOL?
L6         93411 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")
L7             1 SEA ABB=ON  PLU=ON  L4 AND L5 AND L6
                 D L7 1 IBIB ED ABS

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     09 MAR 2015

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L8              SEL PLU=ON  L1 1- CHEM :      65 TERMS
                SET SMARTSELECT OFF

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     09 MAR 2015
L9         93439 SEA ABB=ON  PLU=ON  L8
L10        94160 SEA ABB=ON  PLU=ON  L9 OR DAPSON? OR (DIAMINO(W) DIPHENYL(W)(SU
                 LFON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULFONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULPHONYL]ANILINE")
L11        21262 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
                 MONOETHYL?(W) ETHER?) OR (ETHOXY(W) DIGLYCOL?) OR TRANSCUTOL?
L12       209940 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           86 SEA ABB=ON  PLU=ON  L10 AND L11 AND L12
L14           83 SEA ABB=ON  PLU=ON  L13 AND (WATER? OR (PURIFIED(W) WATER?) OR
                 AQUEOUS?)
L15           75 SEA ABB=ON  PLU=ON  L14 AND (PD<=20131118 OR AD<=20131118)
L16           84 SEA ABB=ON  PLU=ON  L10 (L) L11 (L) L12
L17           82 SEA ABB=ON  PLU=ON  L16 AND (WATER? OR (PURIFIED(W) WATER?) OR
                 AQUEOUS?)
L18           74 SEA ABB=ON  PLU=ON  L17 AND (PD<=20131118 OR AD<=20131118)
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FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 MAR 2015 HIGHEST RN 1657742-35-2
DICTIONARY FILE UPDATES: 8 MAR 2015 HIGHEST RN 1657742-35-2

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http://www.cas.org/legal/infopolicy

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  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

FILE CAPLUS

FILE COVERS 1907 - 9 Mar 2015 VOL 162 ISS 12
FILE LAST UPDATED: 8 Mar 2015 (20150308/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

CAplus includes complete International Patent Classification (IPC) reclassification data for the first quarter of 2015.

CAplus 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: 7 Mar 2015 (20150307/UP). FILE COVERS 1946 TO DATE.

The 2015 MeSH Thesaurus is now available in MEDLINE. See NEWS for further information, including an important message for pharmacovigilance searchers.

The 2015 MEDLINE reload was completed on January 25, 2015. Type HELP RLOAD at an arror (>=) prompt while in MEDLINE for details.

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: 4 March 2015 (20150304/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 9 Mar 2015 (20150309/ED)
Unique MEDLINE content 1948 to present
Emtree thesaurus last updated January 2015

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 comprehenseive results.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 5 Mar 2015 (20150305/PD)
FILE LAST UPDATED: 5 Mar 2015 (20150305/ED)
HIGHEST GRANTED PATENT NUMBER: US8973161
HIGHEST APPLICATION PUBLICATION NUMBER: US20150067746
CA INDEXING IS CURRENT THROUGH 1 Mar 2015 (20150301/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 5 Mar 2015 (20150305/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

USPAT2 includes complete International Patent Classification (IPC) reclassification data for the first quarter of 2015.

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: 5 Mar 2015 (20150305/PD)
FILE LAST UPDATED: 5 Mar 2015 (20150305/ED)
HIGHEST GRANTED PATENT NUMBER: US8973161
HIGHEST APPLICATION PUBLICATION NUMBER: US20150067939
CA INDEXING IS CURRENT THROUGH 1 Mar 2015 (20150301/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 5 Mar 2015 (20150305/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

USPATFULL includes complete International Patent Classification (IPC)
reclassification data for the first quarter of 2015.

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
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PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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	14082955	Filing Date	2013-11-18	Docket Number (if applicable)	19107 (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, 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 (07-09)
Approved for use through 07/31/2012. 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)	2015-05-27
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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Kevin S. Warner	Nonprovisional Application Number (if known):	14082955
Title of Invention:	TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Laura L. Wine/	Date 05/27/2015
Name (Print/Typed) Laura L. Wine	Practitioner Registration Number 68681

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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.
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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 Art. 19 Amd / Ltr to Ex / Rule 70 to Written Opinion

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) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2013/070613	International filing date *(day/month/year)* 18 November 2013 (18-11-2013)
Applicant ALLERGAN, INC.	

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

Form PCT/ISA/220 (July 2010)

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

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Form PCT/ISA/210 (second sheet) (April 2005)

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

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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

Form PCT/ISA/237 (Cover Sheet) (July 2009)

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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 September 2009 (03.09.2009)

PCT

(10) International Publication Number
WO 2009/108147 A1

(51) International Patent Classification:
A61K 8/02 (2006.01)

(21) International Application Number:
PCT/US2008/002549

(22) International Filing Date:
27 February 2008 (27.02.2008)

(25) Filing Language: English

(26) Publication Language: English

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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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, 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: 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.

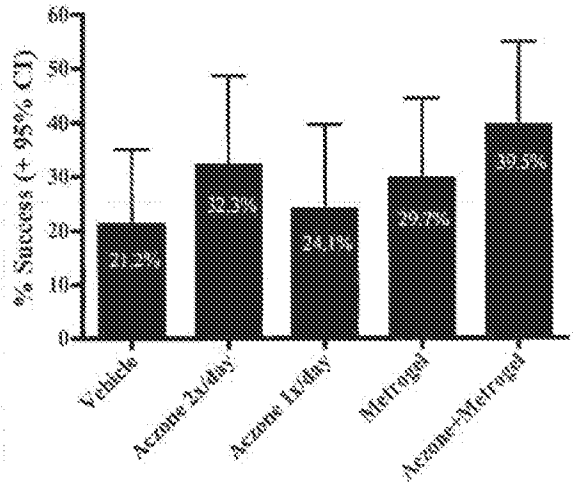

FIG. 11

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 crospolymer, 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 Assesement (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

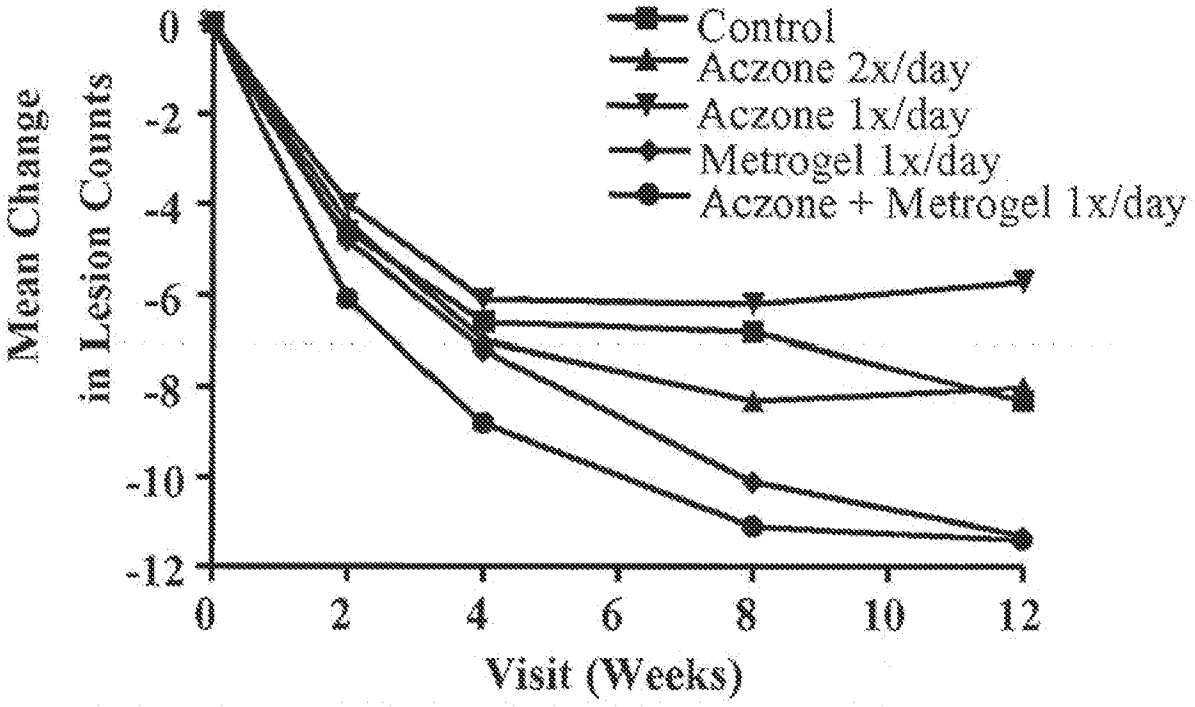
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
0
2
4
6
8
10
12
Visit (Weeks)
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day

FIG. 1

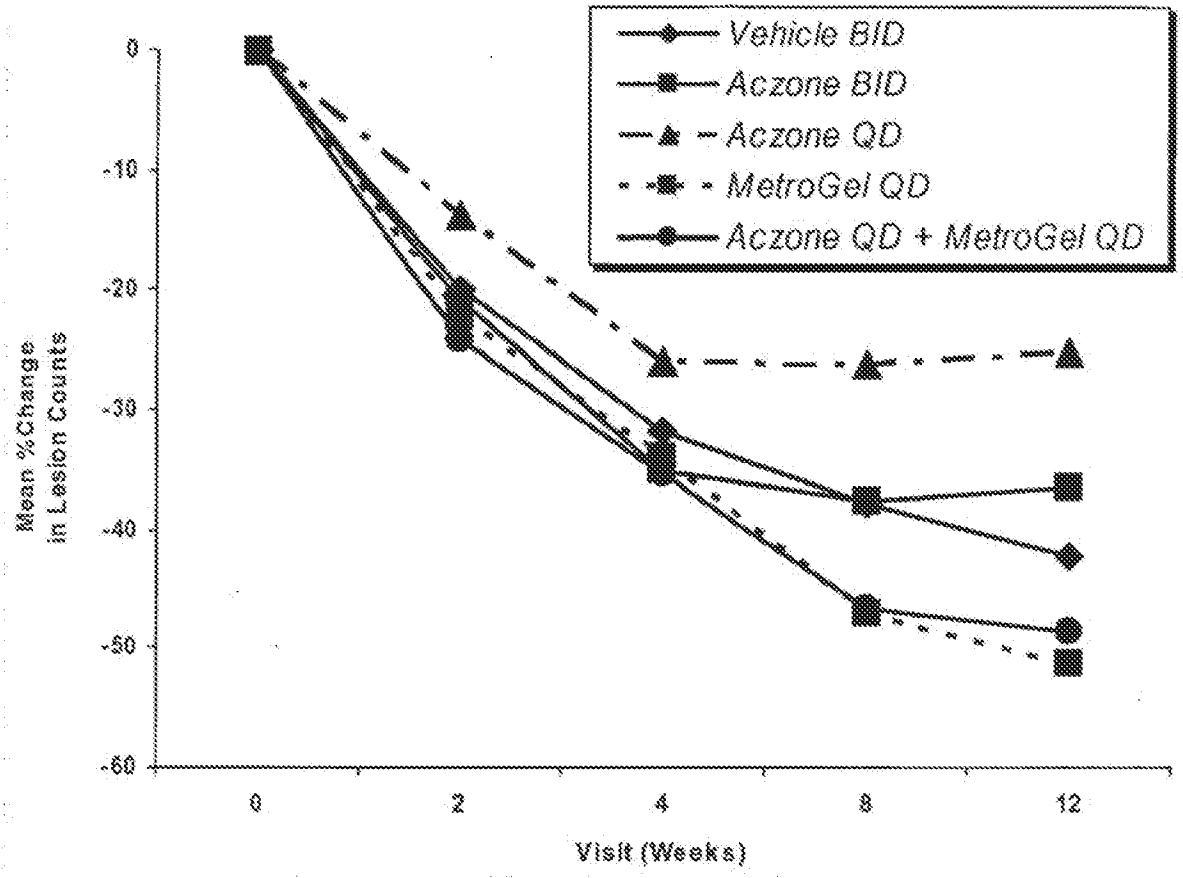
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 2

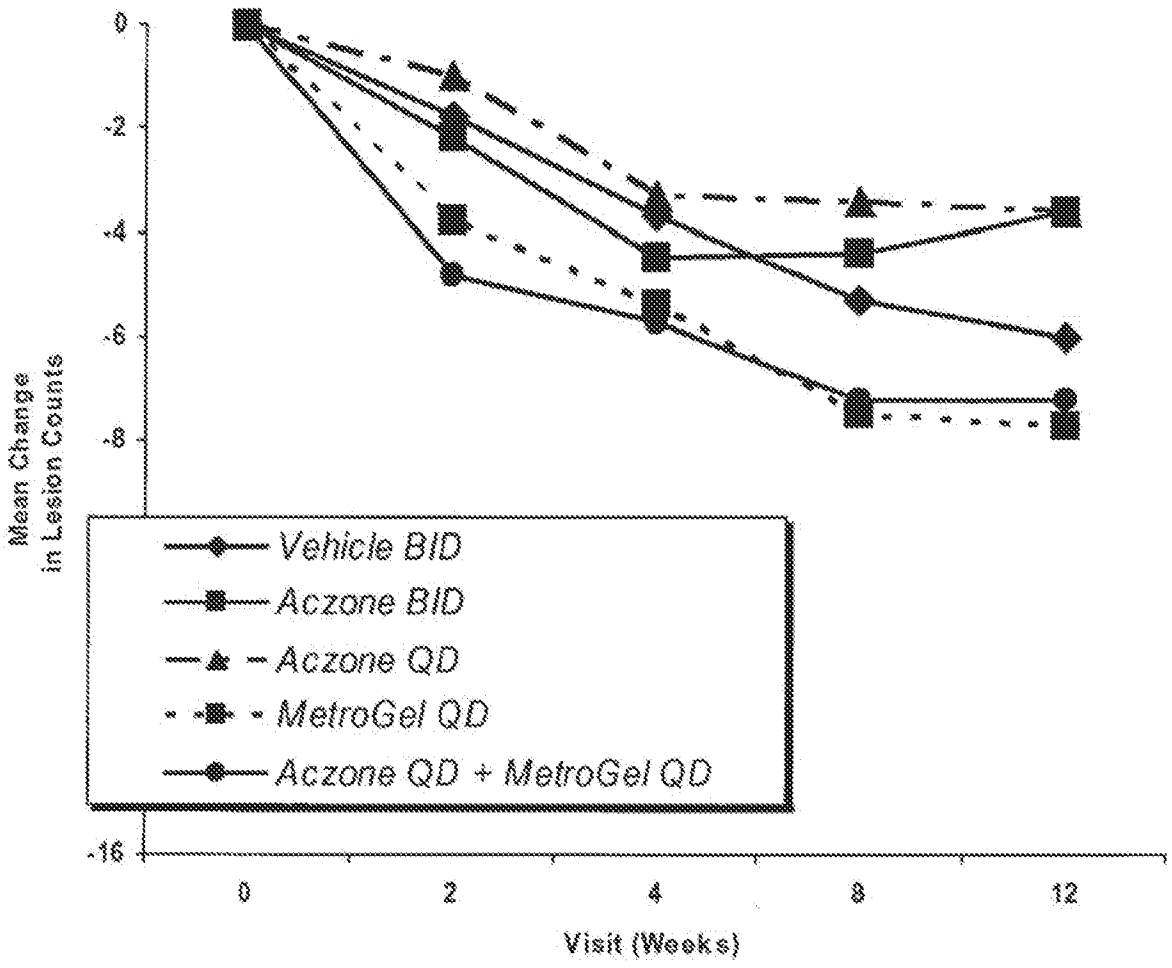
0
-2
-4
-6
-8
-16
Mean Change in Lesion Counts
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
0
2
4
8
12
Visit (Weeks)

FIG. 3

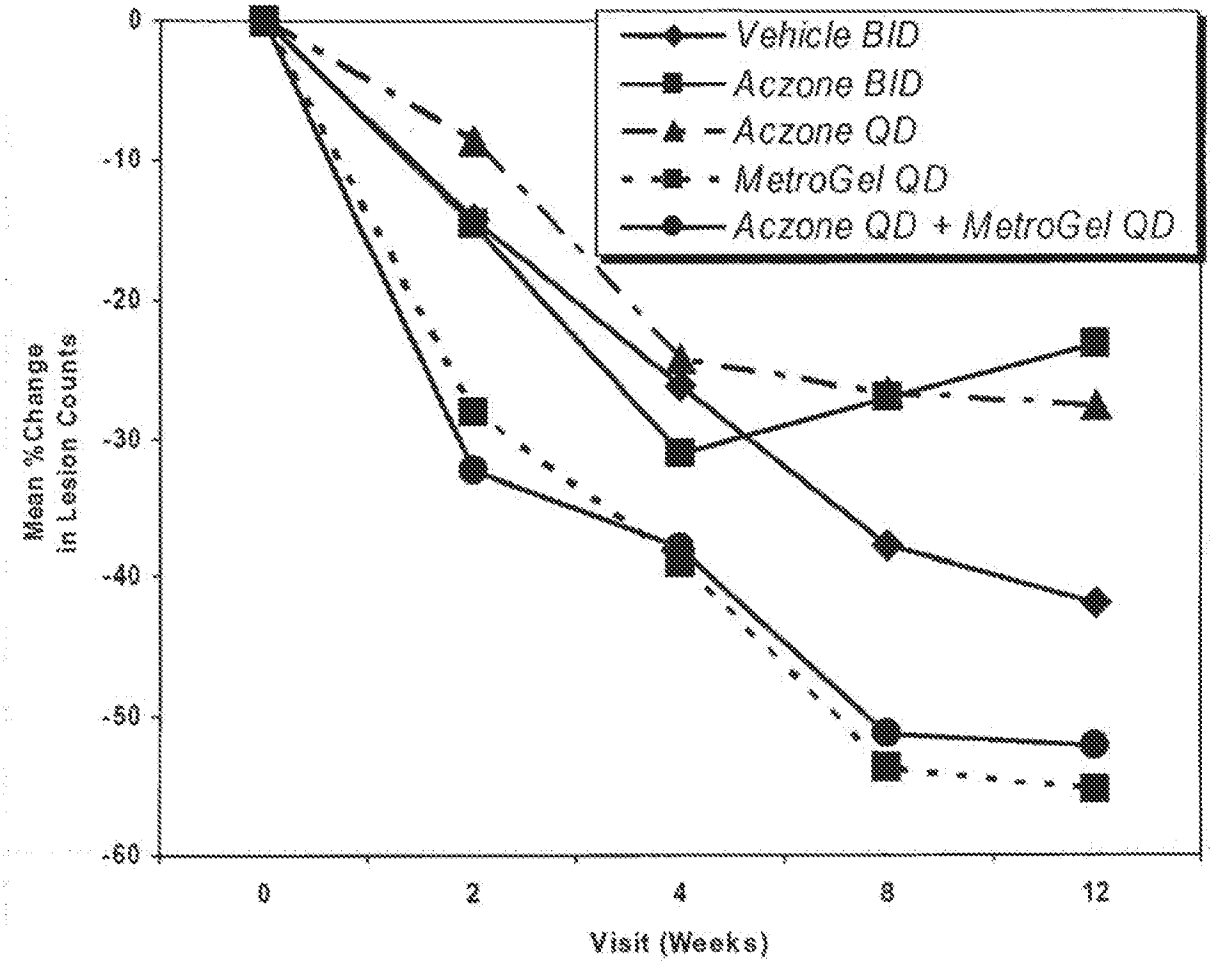
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean % Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 4

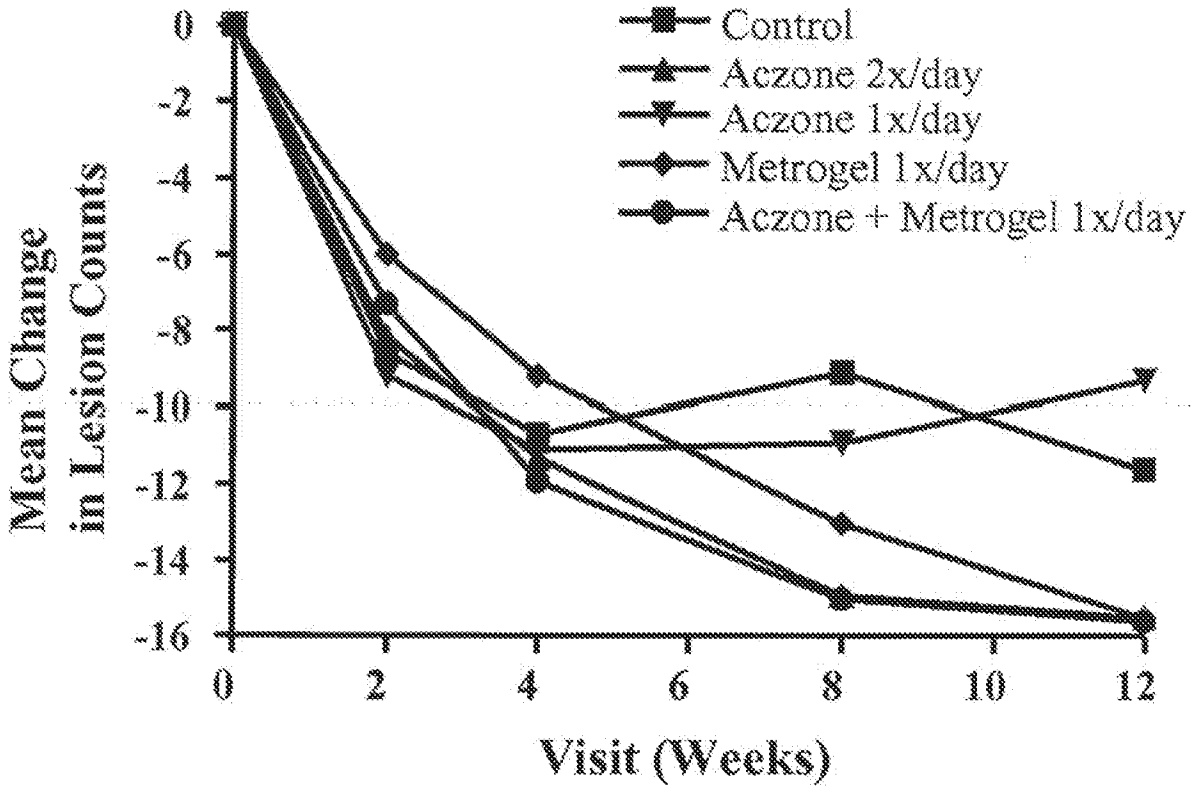
Control
Aczone 2x/day
Aczone 1x/day
Metrogel 1x/day
Aczone + Metrogel 1x/day
Mean Change in Lesion Counts
0
-2
-4
-6
-8
-10
-12
-14
-16
0
2
4
6
8
10
12
Visit (Weeks)

FIG. 5

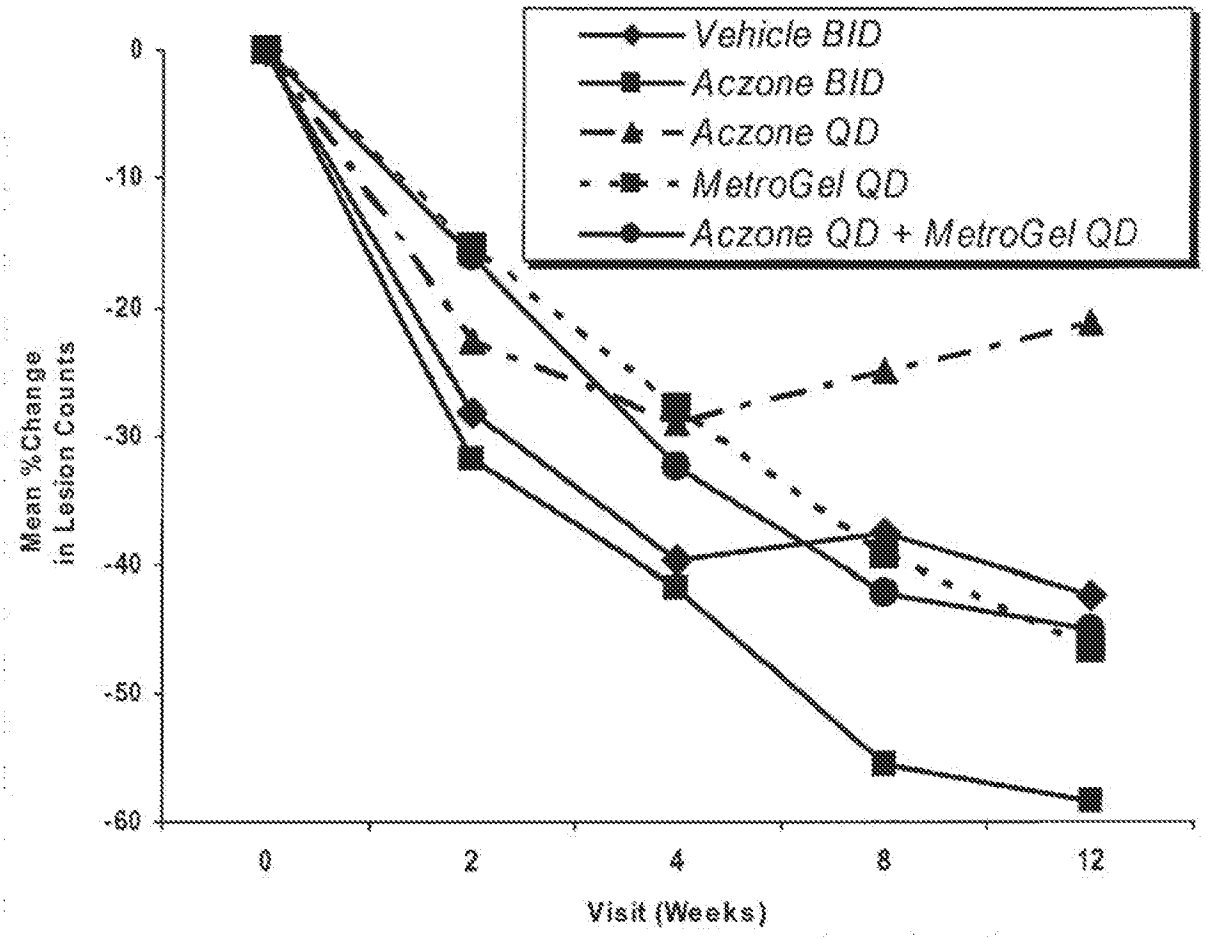
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Mean %Change in Lesion Counts
0
-10
-20
-30
-40
-50
-60
0
2
4
8
12
Visit (Weeks)

FIG. 6

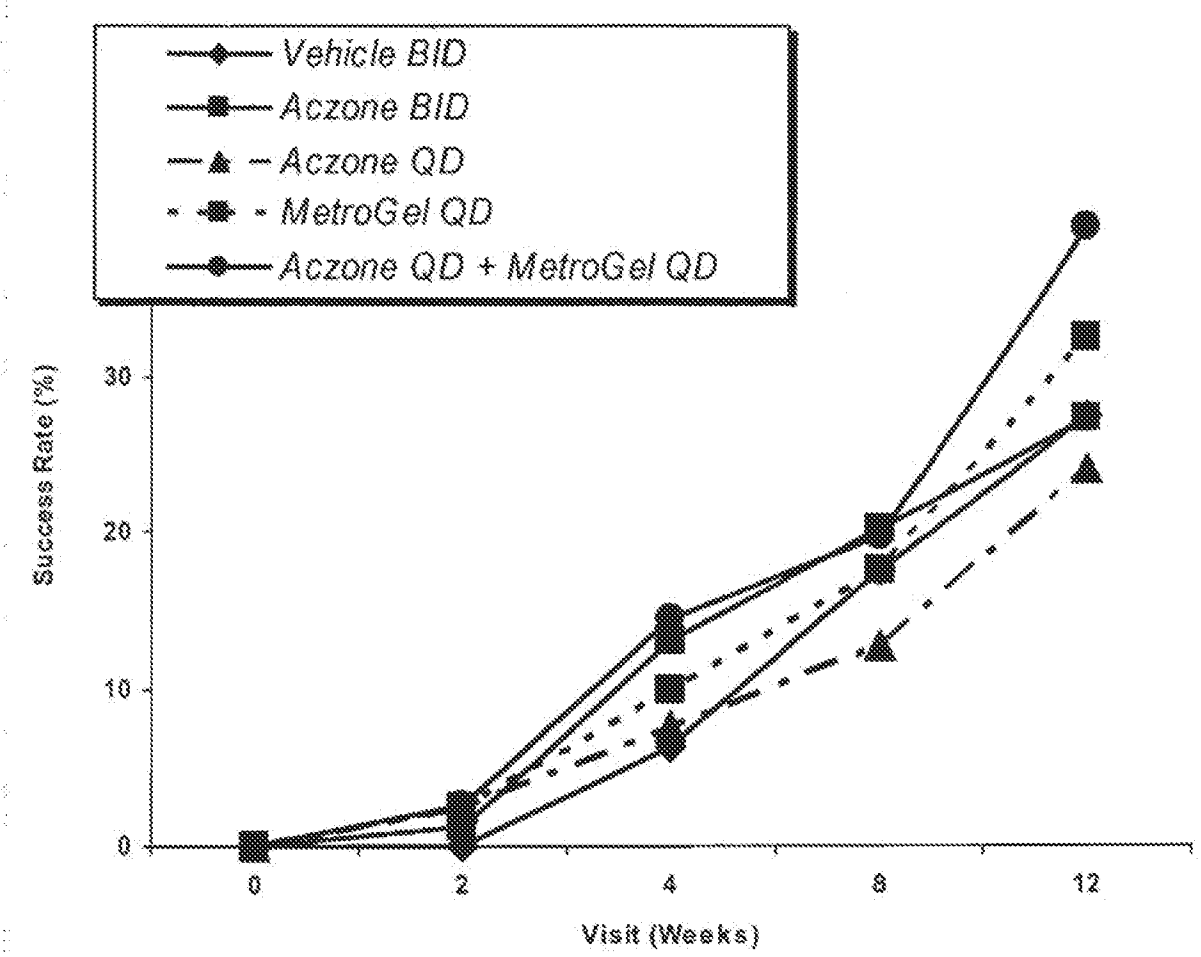
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
Success Rate (%)
0
10
20
30
0
2
4
8
12
Visit (Weeks)

FIG. 7

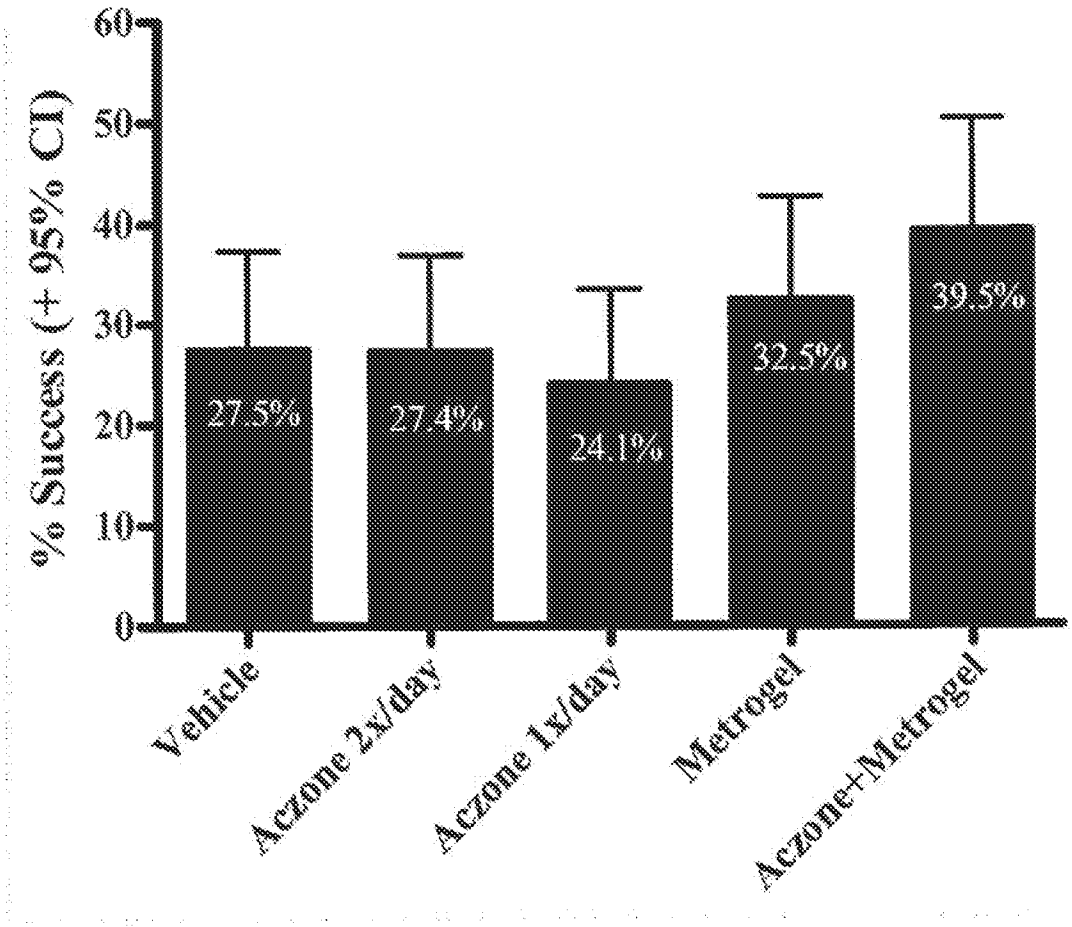
% Success (+ 95% CI)
60
50
40
30
20
10
0
27.5%
27.4%
24.1%
32.5%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

FIG. 8

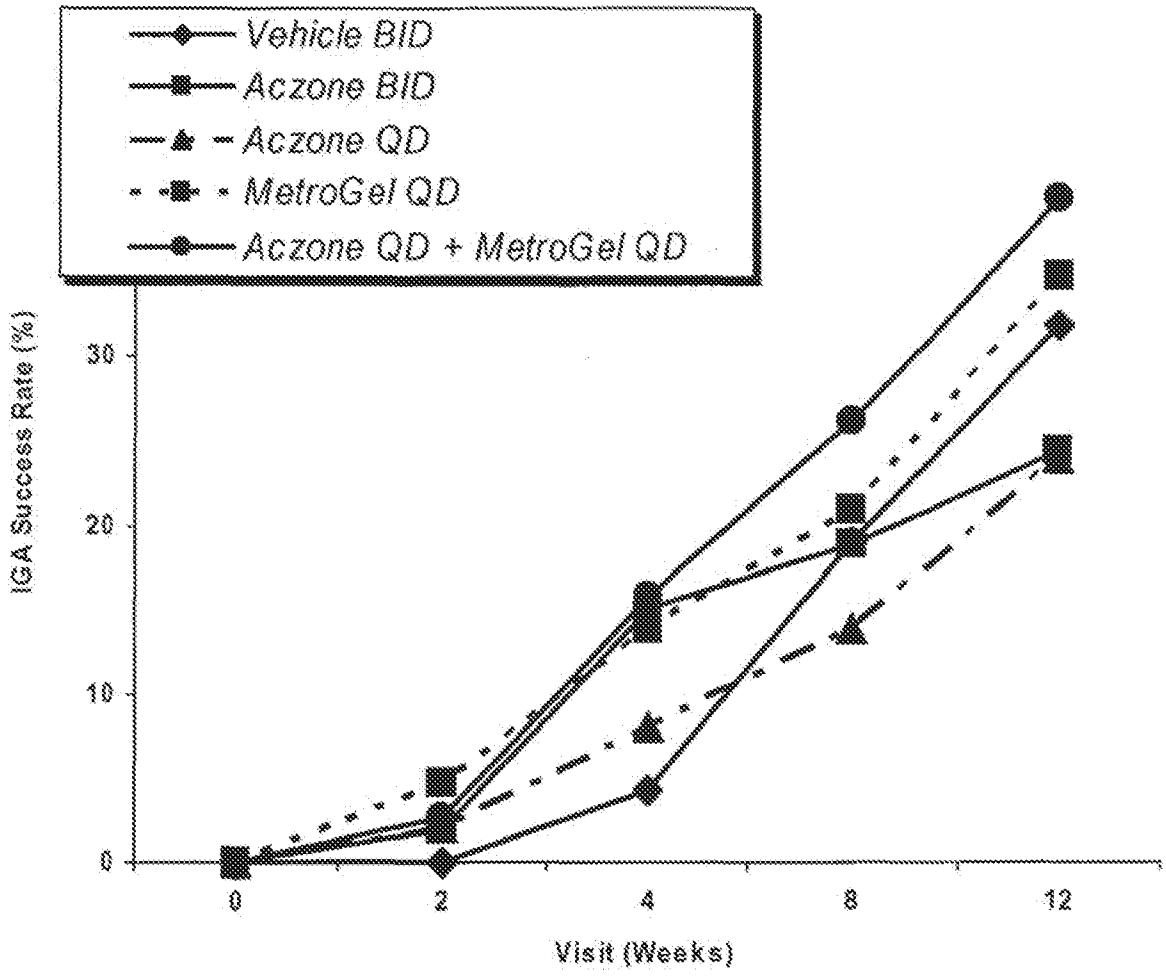
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
0
10
20
30
0
2
4
8
12
Visit (Weeks)

FIG. 9

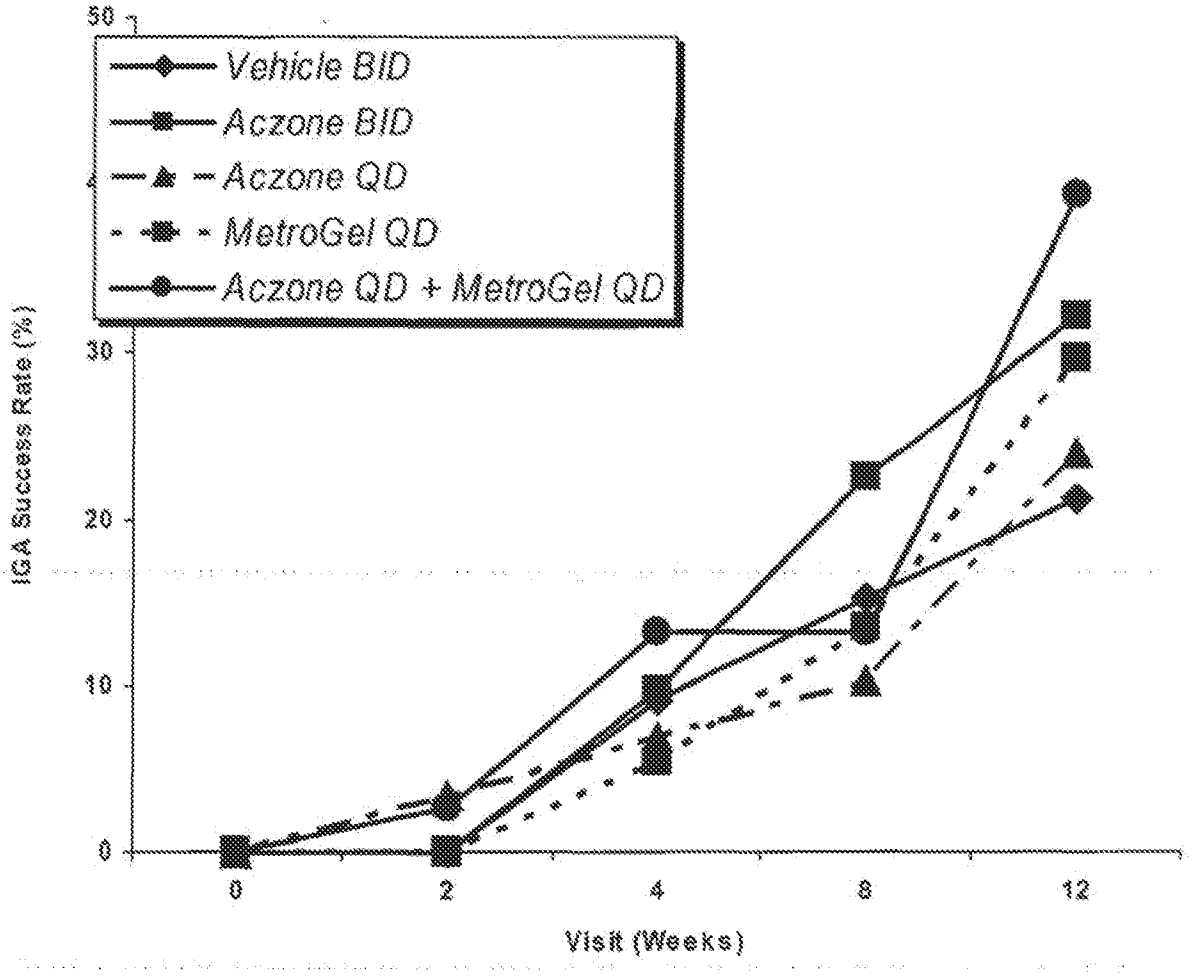
Vehicle BID
Aczone BID
Aczone QD
MetroGel QD
Aczone QD + MetroGel QD
IGA Success Rate (%)
50
30
20
10
0
0
2
4
8
12
Visit (Weeks)

FIG. 10

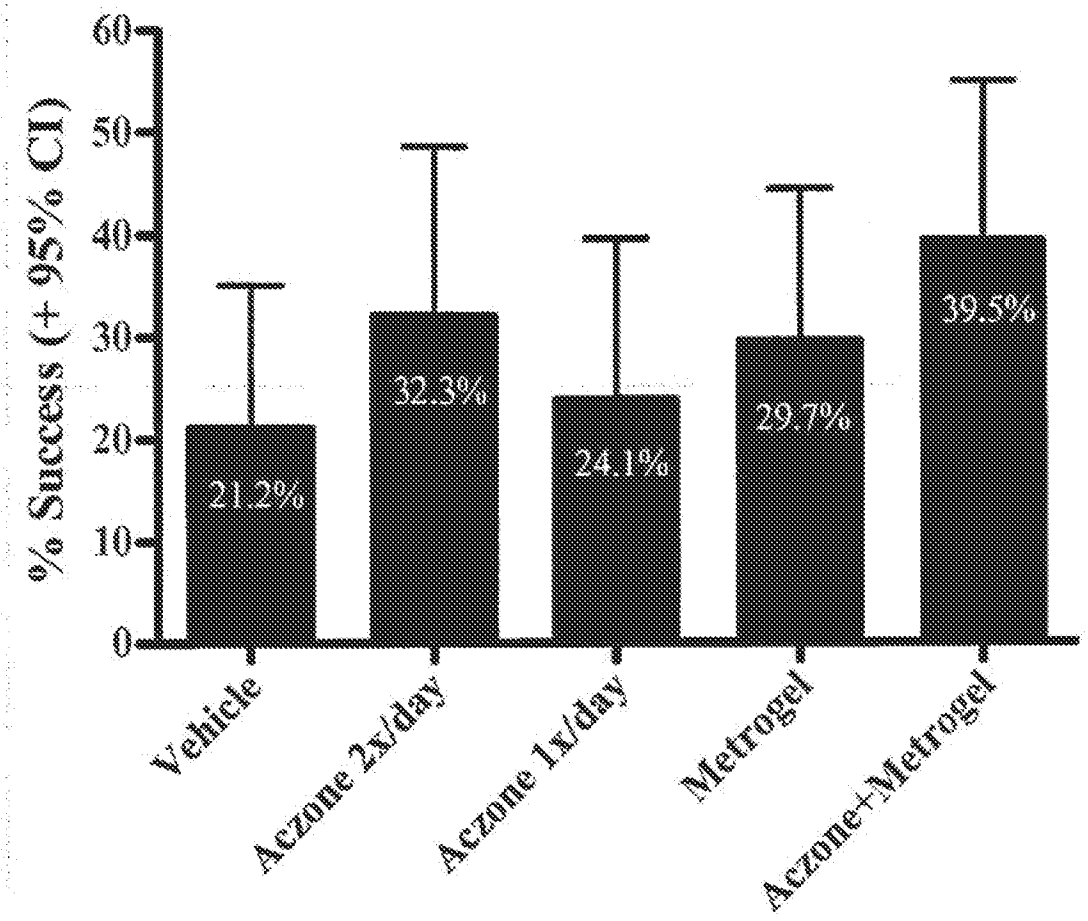
% Success (+ 95% CI)
60
50
40
30
20
10
0
21.2%
32.3%
24.1%
29.7%
39.5%
Vehicle
Aczone 2x/day
Aczone 1x/day
Metrogel
Aczone+Metrogel

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, 648 - 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, 26-33, 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 438, 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

Form PCT/ISA/210 (second sheet) (April 2007)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2011 (03.02.2011)

PCT

(10) International Publication Number
WO 2011/014627 A1

(51) International Patent Classification:
A61K 9/06 (2006.01) *A61K 9/00* (2006.01)
A61K 31/136 (2006.01) *A61P 17/10* (2006.01)
A61K 31/192 (2006.01)

(21) International Application Number:
PCT/US2010/043671

(22) International Filing Date:
29 July 2010 (29.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/229,903 30 July 2009 (30.07.2009) US

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AHLUWALIA, Gurpreet** [US/US]; 3131 Michelson Drive, #303, Irvine, California 92612 (US). **WARNER, Kevin, S.** [US/US]; 1281 N. Walden Lane, Anaheim, California 92807 (US). **CHEN, Haigang** [CN/US]; 1962 Lansdowne Way, Petaluma, California 94954 (US). **YANG, Meidong** [CN/US]; 1400 Pinnacle Court, #204, Richmond, California 94801 (US).

(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-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	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	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	0.95
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	0.7 (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 (3 – 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	15 20
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.

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.	

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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	3		5		3		3		3
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
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

-/--

[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

2

Form PCT/ISA/210 (second sheet) (April 2005)

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
Y	WO 2006/048747 A1 (GLENMARK PHARMACEUTICALS LTD [IN]; CHAUDHARI G N [IN]; KHACHANE V S [I) 11 May 2006 (2006-05-11) page 17; table 1	1-20
Y	WO 2008/017914 A2 (AHUMADA AYALA FERNANDO [MX]) 14 February 2008 (2008-02-14) page 8	1-20
Y	"32258" In: Bundesverband der Pharmazeutischen Industrie: "Rote Liste 2002" 1 January 2002 (2002-01-01), Rote Liste Service GmbH , Frankfurth/Main , XP002606247 the whole document	1-20
X,P	US 2010/029781 A1 (MORRIS JEROME A [US]) 4 February 2010 (2010-02-04) page 4, left-hand column, paragraph 2 claims 1-20	1-20
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

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
US 2007122435 A1	31-05-2007	NONE	
WO 2006048747 A1	11-05-2006	AU 2005300313 A1	11-05-2006
		BR PI0517640 A	14-10-2008
		CA 2586821 A1	11-05-2006
		EP 1841416 A1	10-10-2007
		KR 20070091613 A	11-09-2007
		NZ 555336 A	24-12-2009
		US 2008075776 A1	27-03-2008
		ZA 200704467 A	30-07-2008
WO 2008017914 A2	14-02-2008	EP 2049068 A2	22-04-2009
		US 2009318371 A1	24-12-2009
US 2010029781 A1	04-02-2010	NONE	

Electronic Patent Application Fee Transmittal

Application Number:	14082955
Filing Date:	18-Nov-2013
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:	19107US (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:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
RCE- 2nd and Subsequent Request	1820	1	1700	1700
		Total in USD ($)		**5880**

Electronic Acknowledgement Receipt

EFS ID:	22465066
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	19107US (AP)
Receipt Date:	27-MAY-2015
Filing Date:	18-NOV-2013
Time Stamp:	19:22:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5880
RAM confirmation Number	5737
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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

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	Request for Continued Examination (RCE)	19107AP_RCE.pdf	697606 2de06512d3cbe1335af726af419538028ef47e0c	no	3
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	19107AP_IDS.pdf	595780 90a08a50f7b58d663d1b93c0566d59549014b8e7	no	4
Warnings:					
Information:					
3	TrackOne Request	19107AP_Prioritize_Examination_RCE.pdf	124932 0401be27567aa90f61cd776d26a406977cecb440	no	2
Warnings:					
Information:					
4	Other Reference-Patent/App/Search documents	19107PCT_ISA.pdf	10231964 e3b057f9b202c3cbb53e8ac78141906348fe51c1	no	10
Warnings:					
Information:					
5	Non Patent Literature	Draelos-Two-Randomized-Studies-Demonstrate-2007.pdf	8466333 29bc4469627ff0760776f94a8ce3a0e1582dcc02	no	26
Warnings:					
Information:					
6	Foreign Reference	WO2009-108147.pdf	8041589 24f11395f7c696d0f698bd203900ceb524ebd1a0	no	64
Warnings:					
Information:					
7	Foreign Reference	WO-2011-014627.pdf	4159104 1ebb7843dec22b52fb8487caaa33761f728548e2	no	34
Warnings:					
Information:					

8	Fee Worksheet (SB06)	fee-info.pdf	34005 0bf7c838ac471e37115661311bddaea97db619cc	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	32351313

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.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER KEVIN S
	Art Unit	1629
	Examiner Name	Draper, Leslie A. Royds
	Attorney Docket Number	19107(AP)

U.S.PATENTS Remove

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					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

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	20100029781		2010-02-04	Jerome A. Morris	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	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	2011-014627	WO		2011-02-03	Allergan, Inc.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14082955
	Filing Date	2013-11-18
	First Named Inventor	WARNER KEVIN S
	Art Unit	1629
	Examiner Name	Draper, Leslie A. Royds
	Attorney Docket Number	19107(AP)

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	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 Add

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	14082955
Filing Date	2013-11-18
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107(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.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

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)	2015-05-27
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.

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Commissioner for Patents
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P.O. Box 1450
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www.uspto.gov

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

MAILED
JUN 16 2015
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/082,955

The requisite $140.00 Processing Fee (Fee Code 1830) has been charge to Deposit Account No. 01-0885, pursuant to the deposit account authorization set forth in the documents filed May 27, 2015. Payment of this processing fee is a requirement for acceptance of an application into the Prioritized Examination, Track 1, Program.

1. THE REQUEST FILED May 27, 2015 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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
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NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 07/07/2015

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

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 07/07/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

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	10/07/2015

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 07/07/2015
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.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

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	10/07/2015

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. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

51957 7590 07/07/2015

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

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 07/07/2015

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. 14/082,955	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 27 May 2015*.
   ☐ 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 *1,3,12,13,22 and 23*. 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 27May15
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 11/18/13 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.

EXAMINER'S COMMENT

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 allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). 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, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 27, 2015 has been entered.

Applicant's Information Disclosure Statement (IDS) filed May 27, 2015 has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08 (two pages total), the Examiner has considered the cited references.

Claims 1, 3, 12, 13, 22 and 23 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

June 29, 2015

```
=> d his full

     (FILE 'HOME' ENTERED AT 11:50:23 ON 29 JUN 2015)

     FILE 'REGISTRY' ENTERED AT 11:50:29 ON 29 JUN 2015
                E "DAPSONE"/CN
L1             1 SEA ABB=ON  PLU=ON  DAPSONE/CN
                D L1

     FILE 'HCAPLUS' ENTERED AT 11:50:45 ON 29 JUN 2015

     FILE 'REGISTRY' ENTERED AT 11:51:45 ON 29 JUN 2015
                SET SMARTSELECT ON
L2              SEL PLU=ON  L1 1- CHEM :      65 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 11:51:46 ON 29 JUN 2015
L3         18102 SEA ABB=ON  PLU=ON  L2
L4         18136 SEA ABB=ON  PLU=ON  L3 OR DAPSON? OR (DIAMINO(W)DIPHENYL(W)(SUL
                 FON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULFONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULPHONYL]ANILINE")
L5          4348 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W)GLYCOL(W)MONOETHYL?
                 (W)ETHER?) OR (ETHOXY(W)DIGLYCOL?) OR TRANSCUTOL?
L6         95480 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")
L7             1 SEA ABB=ON  PLU=ON  L4 AND L5 AND L6
                D L7 1 IBIB ED ABS

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:54:00 ON 29 JUN 2015

     FILE 'REGISTRY' ENTERED AT 11:54:04 ON 29 JUN 2015
                SET SMARTSELECT ON
L8              SEL PLU=ON  L1 1- CHEM :      65 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 11:54:05 ON 29 JUN 2015
L9         54055 SEA ABB=ON  PLU=ON  L8
L10        54231 SEA ABB=ON  PLU=ON  L9 OR DAPSON? OR (DIAMINO(W) DIPHENYL(W)(SU
                 LFON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULFONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULPHONYL]ANILINE")
L11         1379 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
                 MONOETHYL?(W) ETHER?) OR (ETHOXY(W) DIGLYCOL?) OR TRANSCUTOL?
L12        47298 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 11:56:48 ON 29 JUN 2015

     FILE 'REGISTRY' ENTERED AT 11:56:51 ON 29 JUN 2015
                SET SMARTSELECT ON
L14             SEL PLU=ON  L1 1- CHEM :      65 TERMS
                SET SMARTSELECT OFF

     FILE 'USPAT2, USPATFULL' ENTERED AT 11:56:52 ON 29 JUN 2015
L15        42116 SEA ABB=ON  PLU=ON  L14
L16        42671 SEA ABB=ON  PLU=ON  L15 OR DAPSON? OR (DIAMINO(W) DIPHENYL(W)(S
                 ULFON? OR SULPHON?)) OR ("4-[(4-AMINOBENZENE)SULFONYL]ANILINE"
                 OR "4-[(4-AMINOBENZENE)SULPHONYL]ANILINE")
L17        20502 SEA ABB=ON  PLU=ON  "DGME" OR (DIETHYLEN?(W) GLYCOL(W)
```

```
                MONOETHYL?(W) ETHER?) OR (ETHOXY(W) DIGLYCOL?) OR TRANSCUTOL?
L18      166631 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")
L19          89 SEA ABB=ON  PLU=ON  L16 AND L17 AND L18
L20          78 SEA ABB=ON  PLU=ON  L19 AND (PD<=20131118 OR AD<=20131118)
L21          77 SEA ABB=ON  PLU=ON  L20 AND (WATER? OR (PURIFIED(W) WATER?) OR
                AQUEOUS?)
L22           7 SEA ABB=ON  PLU=ON  L21 AND (METHYL(W) PARABEN?)
L23           7 DUP REM L22 (0 DUPLICATES REMOVED)
                     ANSWERS '1-2' FROM FILE USPAT2
                     ANSWERS '3-7' FROM FILE USPATFULL
                D L23 1-7 IBIB ABS

     FILE 'HOME' ENTERED AT 11:59:48 ON 29 JUN 2015
                SAVE TEMP ALL L14082955/L


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   28 JUN 2015  HIGHEST RN 1790641-43-8
     DICTIONARY FILE UPDATES:  28 JUN 2015  HIGHEST RN 1790641-43-8

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       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
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     on property searching in REGISTRY, refer to:

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     FILE HCAPLUS

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     FILE COVERS 1907 - 29 Jun 2015 VOL 163 ISS 2
     FILE LAST UPDATED: 28 Jun 2015 (20150628/ED)
     REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Apr 2015
     USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Sep 2014
```

HCAplus includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2015.

HCAplus now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

CAS Information Use Policies apply and are available at:

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This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 28 Jun 2015 (20150628/UP). FILE COVERS 1946 TO DATE.

MEDLINE(R) is a registered trademark of the U.S. National Library of Medicine (NLM).

The 2015 MeSH Thesaurus is now available in MEDLINE. See NEWS for further information, including an important message for pharmacovigilance searchers.

The 2015 MEDLINE reload was completed on January 25, 2015. Type HELP RLOAD at an arror (>=) prompt while in MEDLINE for details.

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: 24 June 2015 (20150624/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 26 Jun 2015 (20150626/ED)
Unique MEDLINE content 1948 to present
Emtree thesaurus last updated May 2015

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 comprehenseive results.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 25 Jun 2015 (20150625/PD)
FILE LAST UPDATED: 25 Jun 2015 (20150625/ED)

HIGHEST GRANTED PATENT NUMBER: US9066461
HIGHEST APPLICATION PUBLICATION NUMBER: US20150181554
CA INDEXING IS CURRENT THROUGH 22 Jun 2015 (20150622/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 25 Jun 2015 (20150625/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

USPAT2 includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2015.

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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: 25 Jun 2015 (20150625/PD)
FILE LAST UPDATED: 25 Jun 2015 (20150625/ED)
HIGHEST GRANTED PATENT NUMBER: US9066461
HIGHEST APPLICATION PUBLICATION NUMBER: US20150181795
CA INDEXING IS CURRENT THROUGH 22 Jun 2015 (20150622/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 25 Jun 2015 (20150625/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2015
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

USPATFULL includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2015.

USPATFULL now includes the comprehensive Cooperative Patent Classification (CPC). See HELP CPC for details.

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www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1222

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/082,955	11/18/2013	514	1629	19107US (AP)

APPLICANTS
ALLERGAN, INC., IRVINE, CA;

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

**** CONTINUING DATA ***************************
This appln claims benefit of 61/728,403 11/20/2012
and claims benefit of 61/770,768 02/28/2013

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
12/02/2013

Drawings filed 11/18/13 are accepted.

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	20	1
Verified and Acknowledged	/LESLIE A ROYDS DRAPER/ Examiner's Signature	Initials				

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	FEES: Authority has been given in Paper	
2320	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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14082955
Filing Date	2013-11-18
First Named Inventor	WARNER KEVIN S
Art Unit	1629
Examiner Name	Draper, Leslie A. Royds
Attorney Docket Number	19107(AP)

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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
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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	20100029781		2010-02-04	Jerome A. Morris	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	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	2011-014627	WO		2011-02-03	Allergan, Inc.		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /LARD/ (06/29/2015)

/Leslie A. Royds Draper/ (06/29/2015)

Receipt date: 05/27/2015	Application Number	14082955 14082955 - GAU: 1629
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2013-11-18
	First Named Inventor	WARNER KEVIN S
	Art Unit	1629
	Examiner Name	Draper, Leslie A. Royds
	Attorney Docket Number	19107(AP)

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	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 Add

EXAMINER SIGNATURE

Examiner Signature	/Leslie A. Royds Draper/ (06/29/2015)	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/ (06/29/2015)

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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
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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)	6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	29 Jun 15	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	WARNER ET AL.
	Examiner	**Art Unit**
	Leslie A. Royds Draper	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
514	646	A	6	1	K	31 / 136 (2006.01.01)	A	6	1	K	31 / 192 (2006.01.01)

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	29 Jun 15	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	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		17												
	2		18												
2	3		19												
	4		20												
	5		21												
	6	5	22												
	7	6	23												
	8		24												
	9		25												
	10		26												
	11		27												
3	12		28												
4	13		29												
	14		30												
	15														
	16														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 6	
/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629 (Primary Examiner)	29 Jun 15 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9011	dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:28
L2	0	"4-[(4-aminobenzene)sulfonyl]aniline" "4-[(4-aminobenzene)sulphonyl]aniline"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:28
L3	23712	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:28
L4	247325	(acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L5	9011	1 or 2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L6	17	5 and 3 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L7	17	6 and (water (purified adj water) aqueous)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L8	25429	"DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L9	17	5 and 8 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29
L10	0	9 not 6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:29

L11	2919	(A61K31/136).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:30
L12	114	11 and (dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:30
L13	45388	(A61K9/0014).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:30
L14	18	12 and 13	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:30
L15	2	14 and (4 and 8)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:31
L16	16	14 not 9	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:31
L17	2	14 and 4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/29 11:31
L18	54	(warner-kevin$).in.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:32
L19	15	(parashar-ajay$).in.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:32
L20	4	(swaminathan-vijaya$).in.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:33
L21	3	(bhatt-varsha$).in.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:33
L22	3892	(allergan$).as.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:33
L23	3943	18 19 20 21 22	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:33
L24	55	23 and (1 2)	US-PGPUB; USPAT; USOCR	OR	OFF	2015/06/29 11:33
L25	2	24 and 3 and 4	US-PGPUB; USPAT;	OR	OFF	2015/06/29 11:33

			USOCR			

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L26	649	(dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L27	1632	("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L28	27195	((acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")).ti,ab,clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L29	596	(dapson$2 (diamino adj2 diphenyl adj2 (sulfon$2 sulphon$2))).clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L30	1615	("DGME" (diethylene adj2 glycol adj2 monoethyl adj2 ether) (ethoxy adj2 diglycol) (transcutol)).clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L31	26363	((acrylamid$2) (acrylamid$2 adj2 sodium adj2 acryloyldimethyl adj2 taurat$2) "sepineo" (sepineo adj2 "600")).clm.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L32	1	29 and 30 and 31	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L33	603	(A61K31/136).CPC.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L34	8573	(A61K9/0014).CPC.	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:35
L35	21	33 and 29	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:36
L36	1	35 and 30 and 31	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:36
L37	12	33 and 34	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:36
L38	5	37 and 29	US-PGPUB; USPAT; UPAD	OR	OFF	2015/06/29 11:36

6/29/2015 11:38:21 AM
C:\Users\lroyds\Documents\EAST\Workspaces\14082955.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14082955	WARNER ET AL.
	Examiner	Art Unit
	Leslie A. Royds Draper	1629

CPC- SEARCHED

Symbol	Date	Examiner
A61K 31/136 (See Attached Text Search Within this Subclass)	03/09/15	LARD
A61K 9/0014 (See Attached Text Search Within this Subclass)	03/09/15	LARD
A61K 31/136 (See Attached Text Search Within this Subclass)	06/29/15	LARD
A61K 9/0014 (See Attached Text Search Within this Subclass)	06/29/15	LARD

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

Class	Subclass	Date	Examiner
514	646 (See Attached Text Search Within this Subclass)	03/09/15	LARD

SEARCH NOTES

Search Notes	Date	Examiner
Inventor Search (PALM Database, eDAN)	03/18/14	LARD
WEST Search (See Attached Search History)	03/18/14	LARD
Updated Inventor Search (PALM Database, eDAN)	06/05/14	LARD
Updated WEST Search (See Attached Search History)	06/05/14	LARD
Updated Inventor Search (PALM Database, eDAN)	11/24/14	LARD
EAST Search (See Attached Search History)	11/24/14	LARD
STN Search (See Attached Search History)	11/24/14	LARD
Updated Inventor Search (PALM Database, eDAN)	03/09/15	LARD
Updated EAST Search (See Attached Search History)	03/09/15	LARD
Updated STN Search (See Attached Search History)	03/09/15	LARD
Updated Inventor Search (PALM Database, eDAN)	06/29/15	LARD
Updated EAST Search (See Attached Search History)	06/29/15	LARD
Updated STN Search (See Attached Search History)	06/29/15	LARD

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	29 June 2015

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
A61K	31/136 (See Attached Text Search within this Subclass)	03/09/15	LARD
A61K	9/0014 (See Attached Text Search within this Subclass)	03/09/15	LARD
514	646 (See Attached Text Search within this Subclass)	03/09/15	LARD
A61K	31/136 (See Attached Text Search within this Subclass)	06/29/15	LARD
A61K	9/0014 (See Attached Text Search within this Subclass)	06/29/15	LARD

/Leslie A. Royds Draper/ Primary Examiner, Art Unit 1629	29 June 2015

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
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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.

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51957 7590 07/07/2015
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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)
September 10, 2015	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	11/18/2013	Kevin S. Warner	19107US (AP)	1222

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	10/07/2015

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 Joel B. German
3 Debra D. Condino

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)
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- ☐ A check is enclosed.
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- ☒ 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 September 10, 2015
Typed or printed name Laura L. Wine Registration No. 68681

Electronic Patent Application Fee Transmittal

Application Number:	14082955
Filing Date:	18-Nov-2013
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:	19107US (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:	23456633
Application Number:	14082955
International Application Number:	
Confirmation Number:	1222
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:	19107US (AP)
Receipt Date:	10-SEP-2015
Filing Date:	18-NOV-2013
Time Stamp:	16:00:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	2762
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)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply 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	Issue Fee Payment (PTO-85B)	19107AP_Form_PTOL85.pdf	160933 577a031ea283e7c5cf845e0ccdc925e76ffb9bcf	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30559 4dd64d7133d73f100533dce791bcf1a58bf347ab	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	191492		

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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.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/082,955	10/20/2015	9161926	19107US (AP)	1222

51957 7590 09/30/2015

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):

ALLERGAN, INC., IRVINE, CA;
Kevin S. Warner, Anaheim, CA;
Ajay P. Parashar, San Diego, CA;
Vijaya Swaminathan, San Francisco, CA;
Varsha Bhatt, San Francisco, CA;