US 20200261402A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2020/0261402 A1

TOLEDANO et al. (43) Pub. Date: Aug. 20, 2020

(54) **METHOD FOR TREATMENT OF MODERATE TO SEVERE ERYTHEMA SYMPTOMS IN ROSACEA PATIENTS**

(71) Applicant: **Sol-Gel Technologies Ltd.**, Ness Ziona, IL (US)

(72) Inventors: **Ofer TOLEDANO**, Kfar Saba, IL (US); **Ofra LEVY-HACHAM**, Ness Ziona, IL (US); **Ori NOV**, Tarum, IL (US); **Vered RAM**, Rehovot, IL (US)

(21) Appl. No.: **16/794,974**

(22) Filed: **Feb. 19, 2020**

Related U.S. Application Data

(60) Provisional application No. 62/977,974, filed on Feb. 18, 2020, provisional application No. 62/977,952, filed on Feb. 18, 2020, provisional application No. 62/972,896, filed on Feb. 11, 2020, provisional application No. 62/972,310, filed on Feb. 10, 2020, provisional application No. 62/960,384, filed on Jan. 13, 2020, provisional application No. 62/925,258, filed on Oct. 24, 2019, provisional application No. 62/871,286, filed on Jul. 8, 2019, provisional application No. 62/871,283, filed on Jul. 8, 2019, provisional application No. 62/807,356, filed on Feb. 19, 2019, provisional application No. 62/807,368, filed on Feb. 19, 2019.

Publication Classification

(51) **Int. Cl.**

A61K 31/327 (2006.01)

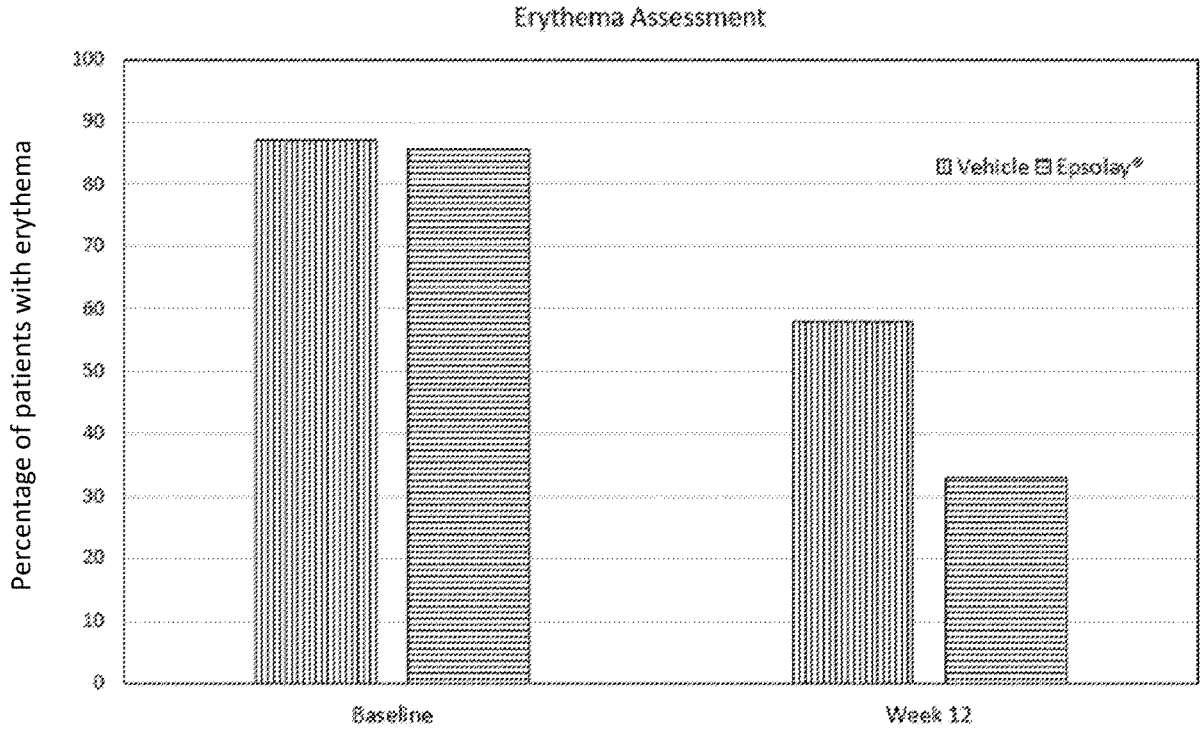
A61P 17/00 (2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/327*** (2013.01); *A61K 9/0014* (2013.01); ***A61P 17/00*** (2018.01)

(57) **ABSTRACT**

A regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 12 weeks, to achieve a percentage decrease of about 60% in a population exhibiting moderate to severe erythema symptoms when measured at about 12 weeks after initial treatment of the population with the pharmaceutical composition.



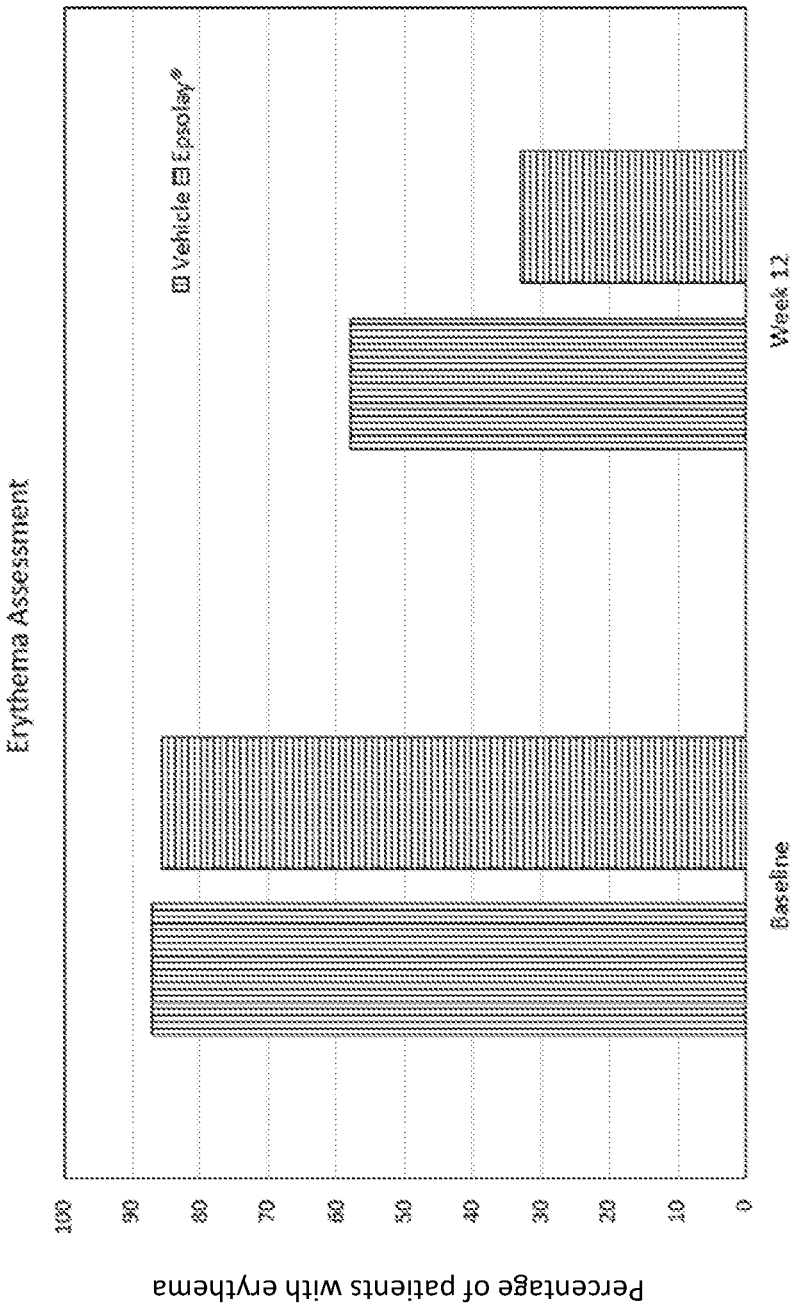

Erythema Assessment
Vehicle
Epsolay®
Baseline
Week 12
Percentage of patients with erythema
100
90
80
70
60
50
40
30
20
10
0

FIGURE 1A

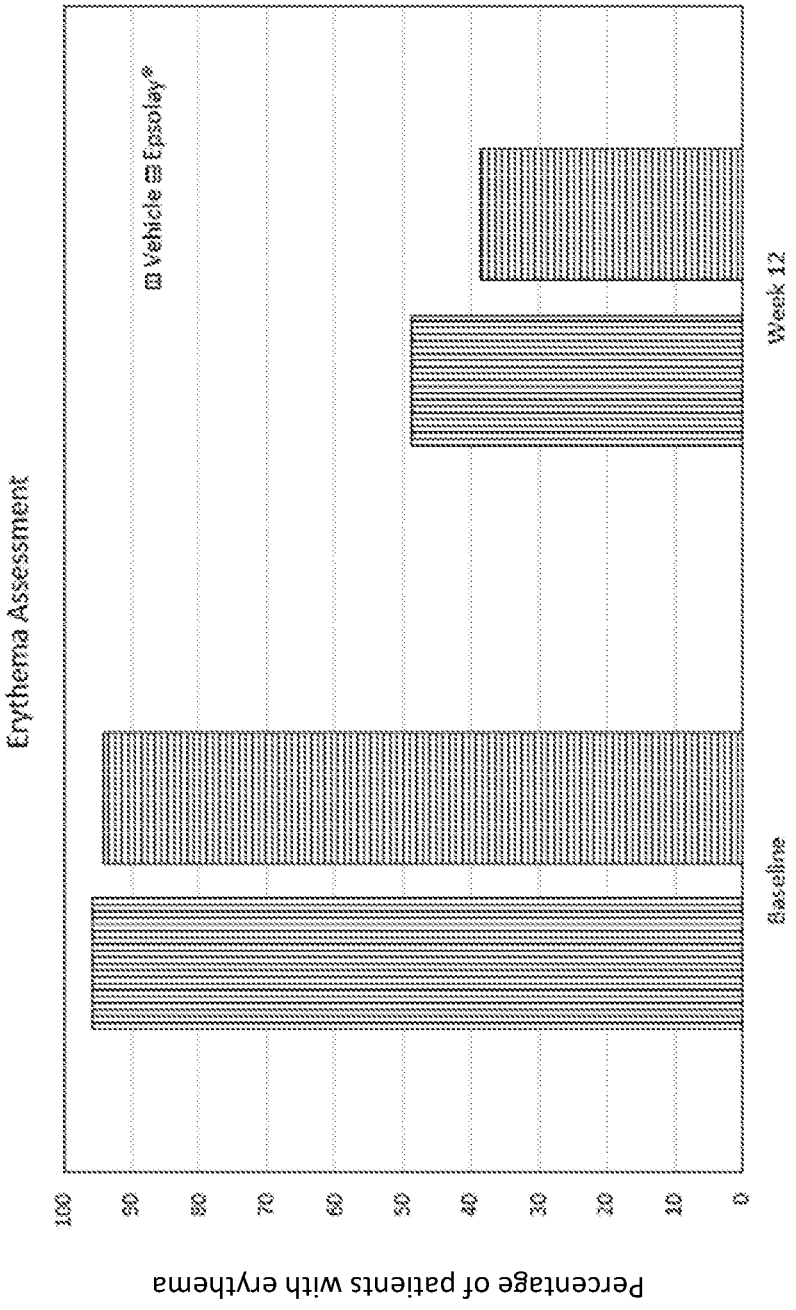

Erythema Assessment
Vehicle
Week 12
Baseline
Percentage of patients with erythema
100
90
80
70
60
50
40
30
20
10
0

FIGURE 1B

METHOD FOR TREATMENT OF MODERATE TO SEVERE ERYTHEMA SYMPTOMS IN ROSACEA PATIENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Application No. 62/977,974, filed Feb. 18, 2020, U.S. Provisional Application No. 62/977,952, filed Feb. 18, 2020, U.S. Provisional Application No. 62/972,896, filed Feb. 11, 2020, U.S. Provisional Application No. 62/972,310, filed Feb. 10, 2020, U.S. Provisional Application No. 62/960,384, filed Jan. 13, 2020, U.S. Provisional Application No. 62/925,258, filed Oct. 24, 2019, U.S. Provisional 62/871,286, filed Jul. 8, 2019, U.S. Provisional 62/871,283, filed Jul. 8, 2019, U.S. Provisional 62/807,356, filed Feb. 19, 2019, and U.S. Provisional 62/807,368, filed Feb. 19, 2019, the contents of which are incorporated in their entirety as if fully set forth herein.

TECHNICAL FIELD

[0002] This application relates to methods for the therapeutic treatment of symptoms and considerations associated with skin conditions and afflictions, such as rosacea, including moderate to severe rosacea, including topically applying to the skin of a subject in need of said treatment a pharmaceutical composition comprising benzoyl peroxide.

BACKGROUND

[0003] Rosacea is a chronic disease of inflammatory dermatitis that mainly affects the median part of the face and the eyelids of certain adults. It is characterized by telangiectatic erythema, dryness of the skin, papules and pustules. Conventionally, rosacea develops in adults from the ages of 30 to 50, and more frequently affects women, although the condition is generally more severe in men. Rosacea is a primitively vascular condition whose inflammatory stage lacks the cysts and comedones characteristic of common acne.

[0004] Factors that have been described as possibly contributing towards the development of rosacea include, for example: the presence of parasites such as the *Demodex folliculorum*; the presence of bacteria such as *Helicobacter pylori* (a bacterium associated with gastrointestinal disorders); hormonal factors (such as endocrine factors); climatic and immunological factors; and so forth.

[0005] Rosacea develops in four stages over several years, in spasms aggravated by variations in temperature, alcohol, spices, exposure to sunlight and stress. The various stages of the disease are:

[0006] Stage 1 (stage of erythema episodes): the patients have erythrosis spasms due to the sudden dilation of the arterioles of the face, which then take on a congestive, red appearance. These spasms are caused by emotions, meals and temperature changes.

[0007] Stage 2 (stage of couperosis, i.e., of permanent erythema with telangiectasia): certain patients also have oedema on the cheeks and the forehead.

[0008] Stage 3 (inflammatory stage, papulopustular rosacea): patients exhibit appearance of inflammatory papules and pustules, but without affecting the sebaceous follicles, and thus, does not include cysts and comedones.

[0009] Stage 4 (rhinophyma stage): this late phase essentially affects men. The patients have a bumpy, voluminous red nose with sebaceous hyperplasia and fibrous reordering of the connective tissue.

[0010] Erythema is a symptom of rosacea, and includes an abnormal and/or superficial reddening and inflammation of the skin, usually localized or patchy, caused by the congestion and dilation of blood capillaries.

[0011] Typical treatment of rosacea includes oral or topical administration of antibiotics such as tetracyclines, salicylic acid, anti-fungal agents, steroids, metronidazole (an anti-bacterial agent) and isotretinoin, or treatment with anti-infectious agents such as azelaic acid.

SUMMARY

[0012] An exemplary embodiment of this application is a regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 12 weeks, to achieve a percentage decrease of about 60% in a population exhibiting moderate to severe erythema symptoms when measured at about 12 weeks after initial treatment of the population with the pharmaceutical composition.

[0013] Another exemplary embodiment of this application is a regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, and wherein after about 2 weeks of treatment with the pharmaceutical composition there is no increase in erythema symptoms.

[0014] In other exemplary embodiments, the number of patients with no erythema symptoms does not increase after treatment for about 2 weeks with the pharmaceutical composition.

[0015] In other exemplary embodiments, the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 10% to about 30% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

[0016] In other exemplary embodiments, the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 18% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

[0017] In other exemplary embodiments, the benzoyl peroxide is the sole active ingredient administered to the subject during the duration of the regimen.

[0018] In other exemplary embodiments, the pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of the benzoyl peroxide.

[0019] In other exemplary embodiments, the pharmaceutical composition comprises about 5% w/w of the benzoyl peroxide.

[0020] In other exemplary embodiments, the benzoyl peroxide is in a solid, solution or suspension form.

[0021] In other exemplary embodiments, the regimen is a first line therapy for the treatment of moderate to severe rosacea.

[0022] In other exemplary embodiments, the moderate to severe rosacea is any of erythematotelengietatic rosacea, papulopustular rosacea, phymatous rosacea or ocular rosacea.

[0023] In other exemplary embodiments, the pharmaceutical composition is a cream or an emulsion.

[0024] In other exemplary embodiments, the pharmaceutical composition is an extended-release formulation.

[0025] In other exemplary embodiments, an extended-release effect from the extended-release formulation is obtained by encapsulation, microencapsulation, microspheres or coating.

[0026] In other exemplary embodiments, the benzoyl peroxide is encapsulated or microencapsulated.

[0027] In other exemplary embodiments, the benzoyl peroxide is included in a microsphere or a coating.

[0028] Details of other exemplary embodiments of the present disclosure will be included in the following detailed description and the accompanying drawings. It is appreciated that certain features of the exemplary embodiments described in this application, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] In order to understand the disclosure and to see how it can be carried out in practice, embodiments will now be described, by way of non-limiting examples only, with reference to the accompanying drawings, in which:

[0030] FIGS. **1**A and **1**B are graphs presenting the percentage of patients with erythema at baseline and after treatment with a BPO composition for a period of about 12 weeks compared with the percentage of patients with erythema after treatment with vehicle alone.

DETAILED DESCRIPTION

[0031] Multiple studies have been directed to the treatment of rosacea using a pharmaceutical or dermatological active agent such as metronidazole, azelaic acid, sulfacetamide, brimonidine, ivermectin, permethrin and clindamycin, and with doxycycline, which is identified as the only FDA-approved treatment for rosacea (Oge et al., "Rosacea: Diagnosis and Treatment," *American Family Physician*, v. 92(3), pp. 187-198 (2015); Gul et al., "A case of granulomatous rosacea successfully treated with pimecrolimus cream," *J. Derm. Treatment,* 19, 313-315 (2008)).

[0032] Benzoyl peroxide (BPO) is generally identified as an anti-acne agent, used alone (U.S. Pat. No. 9,439,857; Wester et al., "Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy," *J. Am. Acad. Derma.* 24, 720-726 (1991); Sawleshwarkar, "Multicenter study to evaluate efficacy and irritation potential of benzoyl peroxide 4% cream in hydrophase base (Brevoxyl) in acne vulgaris," *Ind. J. Derm. Vener. Lepro.,* 69(1), 19-22 (2003)) or in combination with a primary active such as avermectin (U.S. 2011/0052515).

[0033] One such study includes a therapeutic regimen involving treatment of acne rosacea in a group of patients in need of such treatment with 5% BPO-acetone gel for four weeks, followed by treatment of the same group of patients with 10% BPO-acetone gel for an additional four weeks. (Montes et al., "Topical Treatment of Acne Rosacea with Benzoyl Peroxide Acetone Gel," *Therapeutics for the Clinician: New Reports on Treatment Modalities of Possible Interest to Patient-Caring Physicians,* 32, 185-190 (1983)). The Montes study showed a significantly better response during the five to eight weeks of treatment with 10% BPO-acetone gel compared to the first four weeks of treatment with 5% BPO-acetone gel. Moreover, although Montes 1983 claims success in the treatment of rosacea using a BPO-acetone gel, 25% of the patients in the study showed no improvement and 40% of the patients developed an irritation. Additionally, this study required increasing the amount of BPO administered to the patients from 5% to 10% after week four. The results of the Montes 1983 study make it clear that BPO would not be suitable for regular use in the treatment of rosacea, especially as a first line treatment of rosacea.

[0034] Other studies show that, when used in the treatment of rosacea, BPO is generally combined with a primary active agent such as clindamycin (Breneman et al., "Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with severe rosacea," *Int. J. Derm.,* 43, 381-387 (2004); Gold et al., "Use of Benzoyl Peroxide/Clindamycin gel in the once daily treatment of moderate rosacea," *J. Amer. Acad. Dermat.,* 52(3), sup., P25 (2004); Leyden et al., "Blind photographic review for a double blind, multicenter, placebo-controlled study comparing Benzoyl Peroxide/Clindamycin and placebo for the treatment of rosacea," *J. Amer. Acad. Dermat.,* 52(3), sup., P14 (2004); Goldgar et al., "Treatment Options for Acne Rosacea," *J Amer. Fam. Physician,* 80(5), 461-468 (2009)).

[0035] BPO is generally identified as only a possible second-line treatment of rosacea following the use of another, different active. (Oge 2015, Table 5; Goldgar 2009, "Key Recommendations for Practice"). Goldgar 2009, in particular, recommends the use of BPO only as a tertiary therapy for the treatment of rosacea.

[0036] When BPO was used as the sole active agent for the treatment of rosacea, lesions were found to be unresponsive. (Gul 2008).

[0037] These previous rosacea treatments with BPO alone or in combination with other agents, have been shown to have several drawbacks such as irritation and intolerance phenomena, especially when they are administered for a prolonged period. (Crawford et al., "Rosacea: I. Etiology, pathogenesis, and subtype classification," *J. Am. Acad. Dermatol.,* 51, 327-341 (2004)). These treatments are only suppressive and not curative, acting especially on the pustulous spasms occurring during the inflammatory stage.

[0038] Such drawbacks associated with the treatment of rosacea involving the use of BPO result in exclusion of BPO from standard rosacea treatment methods. For example, A Review of the Current Modalities for the Treatment of Papulopustular Rosacea identifies metronidazole, ivermec-

tin and azelaic acid as topical therapies that were proven effective for the treatment of rosacea. (McGregor et al., "A Review of the Current Modalities of the Treatment of Papulopustular Rosacea," *Dermatol. Clin.* (2017)). While McGregor 2017 mentions alternate therapies, such as sodium sulfacetanide/sulfur cream, clindamycin, tretinoin, calcineurin inhibitors and oral tretinoin, that may have some effectiveness in the treatment of rosacea, notably, McGregor 2017 does not include BPO in the long list of possible treatment therapies described therein. The absence of BPO as a known treatment for rosacea is also evident in other studies. (Feaster et al., "Clinical effectiveness of novel rosacea therapies," Current Op. Pharmacol., 46, 14-18 (2019); Del Rosso et al., "Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS); *J. Clinical & Aesthetic Dermat.,* 12 (6), 17-24 (2019)). The absence of BPO as a recognized first-line treatment for rosacea is especially evident in Del Rosso, which is a well-known and respected authority on the treatment of rosacea. The AARS review lists the Society's recommendation for rosacea treatment, including topical metronidazole, topical azelaic acid, oral tetracyclines, ivermectin, topical alpha agonists, and oral isotretinoin, as well as "alternative therapies," such as sulfacetamide/sulfur, calcineurin inhibitors, retinoids, and permethrin. (See e.g., Table 1 of the AARS review.) BPO is not mentioned in the AARS review either as a leading or an alternative therapeutic agent for the treatment of rosacea.

[0039] Considering the chronic nature of rosacea, there is a need for early onset of action, and a prolonged use and/or treatment of the disease, its symptoms and associated conditions, in a safe and effective manner. Thus, there exists a need for compositions that show early onset of action, and improved efficacy in the treatment of rosacea, that impart greater tolerance to the active principles and that reduce, substantially minimize or do not have the side effects described in the prior art.

[0040] Advantages and features of the present disclosure, and methods for accomplishing the same will be more clearly understood from exemplary embodiments described below with reference to any accompanying drawings and figures. However, the present disclosure is not limited to the following exemplary embodiments and can be implemented in various different forms. The exemplary embodiments are provided only to provide sufficient disclosure of the present discoveries and to fully provide a person having ordinary skill in the art to which the present disclosure pertains within the technical field, and the present disclosure will be defined by any appended claims and combinations thereof.

[0041] As used herein, like reference numerals generally denote like elements throughout the present specification. Further, in the following description, a detailed explanation of well-known related technologies can be omitted to avoid unnecessarily obscuring the subject matter of the present disclosure.

[0042] As used herein, terms such as "including" and "having" are generally intended to allow other components to be included unless the terms are used in conjunction with the term "only."

[0043] As used herein, the term "topical use" is meant to encompass the topical administration of an exemplary composition by formulating said composition in any way known in the art, or in formulations disclosed herein, which are compatible with the skin, mucous membranes and/or the integuments.

[0044] As used herein, the term "treating" or "treatment" includes curing a condition, treating a condition, preventing or substantially preventing a condition, treating symptoms of a condition, curing symptoms of a condition, ameliorating, reducing and/or minimizing symptoms of a condition, treating effects of a condition, ameliorating, reducing and/or minimizing effects of a condition, and preventing and/or substantially preventing results of a condition.

[0045] As used herein, the term "first-line therapy" or "first-line treatment" means a therapy or treatment for which its label does not include a requirement or recommendation that said therapy or treatment should be used only after other therapies or treatments were shown to be unsatisfactory or unsuccessful. It can also include a therapy and/or treatment wherein no other actives (beyond the main active) are administered to the individual subject in need.

[0046] As used herein, the term "success rate" corresponds to a percentage increase in the number of subjects achieving clear or almost clear skin on the investor global assessment (IGA) scale after treatment with the pharmaceutical composition.

[0047] As used herein, the term "early onset" or "early onset of action" means achieving a desired result and/or effect at a point in time that is earlier or even much early than achieved using a vehicle or other, conventional treatment approach. For example, it can mean achieving a desired result and/or effect no later than about 8 weeks from initial treatment, preferably no later than about 4 weeks from initial treatment, and more preferably no later than about 2 weeks from initial treatment.

[0048] As used herein, the term "pharmaceutical composition" refers to a composition comprising one or more active ingredients with other components such as, for example, pharmaceutically acceptable ingredients and/or excipients. The purpose of a pharmaceutical composition is to facilitate administration of an active ingredient to a subject.

[0049] As used herein, the terms "pharmaceutically active agent" or "active agent" or "active pharmaceutical ingredient" are interchangeable and mean the ingredient is a pharmaceutical drug, which is biologically- and/or chemically-active and is regulatory-approved or approvable as such.

[0050] As used herein, the term "ingredient" refers to a pharmaceutically acceptable ingredient, which is included or is amenable to be included in The FDA's Inactive Ingredient (IIG) database. Inactive ingredients can sometimes exhibit some therapeutic effects, although they are not drugs.

[0051] As used herein, the term "adverse events values" refers to an average percentage of subjects that experience any adverse events associated with the treatment of rosacea with a composition described and/or claimed herein (usually on a surface of the skin of a subject treated with a composition described and/or claimed herein). A non-limiting list of such adverse events includes: irritation, dryness, scaling, itching purities, burning, stinging, combinations thereof and the like.

[0052] As used herein, the term "inflammatory lesion" refers to papules and pustules present on the skin of a patient, and does not include nodules and cysts.

[0053] As used herein, the term "papule" refers to a solid, elevated inflammatory lesion equal to or less than about 5 mm in diameter.

[0054] As used herein, the term "pustule" refers to an elevated inflammatory, pus-containing lesion equal to or less than about 5 mm in diameter.

[0055] As used herein, the term "nodule" and/or "cyst" refers to palpable solid inflammatory lesion, greater than about 5 mm in diameter. The nodule and/or cyst may have depth but does not necessarily include elevation.

[0056] Whenever a numerical range is indicated herewith, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicated number and a second indicated number and "ranging/ranges from" a first indicated number "to" a second indicated number are used herein interchangeable and are meant to include the first and second indicated numbers and all fractional and integral numerals therebetween.

[0057] The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a dimension disclosed as "10 μm" is intended to mean "about 10 μm."

[0058] As used herein, numbers and/or numerical ranges preceded by the term "about" should not be considered to be limited to the recited range. Rather, numbers and/or numerical ranges preceded by the term "about" should be understood to include a range accepted by those skilled in the art for any given element in formations according to the subject invention.

[0059] As used herein, when a numerical value is preceded by the term "about," the term "about" is intended to indicate +/−10%.

[0060] As used herein, the singular form "a," "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" can include a plurality of compounds, including combinations and/or mixtures thereof.

[0061] As used herein, the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, technical and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

[0062] It is appreciated that certain features of the exemplary embodiments described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the exemplary embodiments, which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0063] An exemplary embodiment of this application is a regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 12 weeks, to achieve a percentage decrease of about 60% in a population exhibiting moderate to severe erythema symptoms when measured at about 12 weeks after initial treatment of the population with the pharmaceutical composition.

[0064] In another exemplary embodiment, the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 10% to about 30% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

[0065] In another exemplary embodiment, the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 18% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

[0066] Another exemplary embodiment of this application is a regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, and wherein after about 2 weeks of treatment with the pharmaceutical composition there is no increase in erythema symptoms.

[0067] In other exemplary embodiments, the benzoyl peroxide is the sole active ingredient administered to the subject during the duration of the regimen.

[0068] In other exemplary embodiments, the pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of benzoyl peroxide, preferably about 3% to about 9%, about 4% to about 8%, and more preferably about 5% w/w of benzoyl peroxide.

[0069] In other exemplary embodiments, the benzoyl peroxide is selected from solid, solution or suspension form.

[0070] In other exemplary embodiments, the regimen is a first line therapy for the treatment of rosacea.

[0071] In other exemplary embodiments, the rosacea is any one of erythematotelengietatic rosacea, papulopustular rosacea, phymatous rosacea or ocular rosacea.

[0072] In other exemplary embodiments, the rosacea is moderate to severe rosacea, preferably severe rosacea.

[0073] In other exemplary embodiments, the pharmaceutical composition is a cream or an emulsion.

[0074] In other exemplary embodiments, the pharmaceutical composition is an extended release formulation. The extended-release effect can be obtained by encapsulation, microencapsulation, microspheres or coating. The benzoyl peroxide can be encapsulated or microencapsulated, the benzoyl peroxide can be included in a microsphere or a coating, and the like.

[0075] In some further embodiments, the composition further comprises at least one non pharmaceutical active

additive selected from the group consisting of chelating agents, antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants, dyes, mineral or organic acids or bases, fragrances, essential oils, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, calmatives and skin-protecting agents, pro-penetrating agents and gelling agents, or a mixture and/or combination thereof.

[0076] In other embodiments, the composition is formulated into a topically applicable, physiologically acceptable medium comprising of: (a) at least one member selected from the group consisting of water, alcohols, oils, fatty substances and waxes; and (b) at least one additive selected from the group consisting of chelating agents, antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants, dyes, mineral acids, mineral bases, organic acids, organic bases, fragrances, essential oils, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, calmatives, skin-protecting agents, pro-penetrating agents, gelling agents, emulsifiers, co-emulsifiers, and mixtures and/or combinations thereof.

[0077] In some embodiments the composition is formulated as an emulsion (including an oil-in-water emulsion, a water-in-oil emulsion, multiple emulsions and microemulsions). In other embodiments, the composition is formulated as a cream.

[0078] The compositions described in exemplary embodiments herein are pharmaceutical compositions, and especially dermatological compositions, which can be in any galenical form conventionally used for topical application. By addition of a fatty or oily phase, they can also be in the form of dispersions of the lotion or serum type, emulsions of liquid or semi-liquid consistency of the milk type obtained by dispersing a fatty phase in an aqueous phase (O/W) or conversely (W/O), or suspensions or emulsions of soft, semiliquid or solid consistency of the cream, gel or ointment type, or alternatively multiple emulsions (W/O/W or O/W/O), microemulsions, microcapsules, microparticles and/or vesicular dispersions of ionic and/or nonionic type, and/or wax/aqueous phase dispersions. These compositions are formulated according to the usual methods.

[0079] In further embodiments, the composition comprises, as a single pharmaceutical active agent, benzoyl peroxide in a solid form, for topical use in the treatment of rosacea, is an oil in water emulsion comprising a polyoxylstearate and a glycerylstearate. Various methods for the preparation of the BPO-containing compositions are described in U.S. Application Publication Nos. 2010/0016443, 2017/0281571 and 2018/0147165 and U.S. Pat. No. 9,687,465.

[0080] In some embodiments, the ratio of said polyoxylstearate to said glycerylstearate is in the range of about 0.1:10 to about 10:0.1.

[0081] In yet further embodiments, said polyoxylstearate is selected from the group consisting of Polyoxyl-8 stearate, Polyoxyl-20 stearate, Polyoxyl-40 stearate, Polyoxyl-100 stearate and combinations and/or mixtures thereof.

[0082] In further embodiments, said glycerylstearate is selected from the group consisting of glyceryl mono-stearate, glyceryl di-stearate and combinations and/or mixtures thereof.

[0083] In other embodiments, said polyoxylstearate in said composition is in the range of from about 0.1% w/w to about 30% w/w.

[0084] In further embodiments, the amount of said glycerylstearate in said composition is in the range of from about 0.1% w/w to about 30% w/w.

[0085] In other embodiments, said composition further comprises at least one fatty alcohol.

[0086] In other embodiments, said at least one fatty alcohol is selected from the group consisting of octyl alcohol, 2-ethyl hexanol. nonyl alcohol, decyl alcohol, undecanol, dodecyl alcohol, tridecyl alcohol, tetradecyl alcohol, pentadecyl alcohol, cetyl alcohol, palmitoleyl alcohol, heptadecyl alcohol, cetostearyl alcohol, stearyl alcohol, isostearyl alcohol, elaidyl alcohol, oleyl alcohol, linoleyl alcohol, elaidolinolenyl alcohol, ricinoleyl alcohol, nonadecyl alcohol, arachidyl alcohol, heneicosyl alcohol. behenyl alcohol, erucyl alcohol, lignoceryl alcohol, ceryl alcohol, montanyl alcohol, cluytyl alcohol, myricyl alcohol, melissyl alcohol, geddyl alcohol, cetearyl alcohol and combinations and/or mixtures thereof.

[0087] In further embodiments, the amount of said at least one fatty alcohol in said composition is in the range of from about 0.2% w/w to about 50% w/w.

[0088] In yet other embodiments, said composition further comprises a polyacrylic acid homopolymer or copolymer.

[0089] In other embodiments, said oil in said oil in water emulsion is selected from the group consisting of paraffin oil, isopropyl myristate, caprylic/capric triglyceride, squalane, squalene, almond oil, castor oil, olive oil, jojoba oil, sunflower oil, soybean oil, grape seed oil, dimethicone, cyclomethicone and combinations and/or mixtures thereof.

[0090] In further embodiments, said oil in present in the composition in an amount in the range of from about 0.05% w/w to about 50% w/w.

[0091] In some embodiments, said water in said oil in water emulsion further comprises at least one water soluble humectant.

[0092] In other embodiments, said at least one water soluble humectant is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol-X and combinations and/or mixtures thereof, where X is in the range of from about 200 to about 10,000.

[0093] In some embodiments, the composition comprises said solid BPO in a controlled and/or slowed release drug delivery system. In further embodiments, said controlled and/or slowed release drug delivery system is an encapsulation in a microcapsule, wherein said solid BPO is embedded in said microcapsule. When referring to a "controlled and/or slowed release drug delivery system" it should be understood to relate to a delivery system (which in the present application is a topical delivery system) that enables the release of the pharmaceutical active agent in predetermined amounts over a specified period. In some embodiments, said system is a core-shell system of a microcapsule and/or a porous matrix structure, such as, for example, a microsponge. The term "embedded" should be understood to encompass an inert system that provides a barrier between the pharmaceutical active agent, i.e. BPO, and its surrounding environment in the composition. In some embodiments, said agent is entrapped and/or encapsulated in said controlled release system.

[0094] In some embodiments, said core of said microcapsule comprises or consists of said solid BPO.

[0095] In some further embodiments, said microcapsules are a core shell microcapsule. The shell comprises at least

one inorganic polymer. In some other embodiments, said inorganic polymer of said shell is a metal oxide or semi-metal oxide shell (layer).

[0096] In some embodiments, said microcapsule comprises a metal oxide or semi-metal oxide coating or layer (shell) and a core comprising or consisting of solid BPO.

[0097] In some embodiments, said microcapsule comprises a metal oxide or semi-metal oxide coating or layer (shell) and a core comprising solid BPO is prepared by a process comprising the steps of:

[0098] (a) contacting a solid BPO particulate matter with an ionic additive and an aqueous medium to obtain a dispersion of said particulate matter having positive charges on its surface;

[0099] (b) subjecting the particulate matter to a coating procedure comprising precipitating a metal oxide salt onto the surface of the particulate matter to form a metal oxide layer thereon thereby to obtain particulate matter coated by a metal oxide coating layer;

[0100] (c) repeating step (b) at least 4 more times: and

[0101] (d) aging said coating layer.

[0102] As used herein, the term "solid BPO particulate matter" refers to a solid BPO having solubility in water of less than about 1% w/w, typically less than about 0.5% and at times less than about 0.1% w/w at room temperature (about 20° C.). The "solid BPO particulate matter" constitutes the "core" of the particles obtained by the process. The solid BPO particulate matter, is, in some embodiments, in such a state of subdivision that it can be suspended in water, e.g., in the form of a finely-divided powder having a D_{90} (see definition below), in some embodiments in the range of from about 0.3 to about 50 microns. Such a particulate matter can be readily suspended in an aqueous systems by stirring, with or without the aid of a surfactant.

[0103] The terms "solid BPO particulate matter" and "particulate matter" will be used interchangeably.

[0104] In the present application, the terms "layer", "coating" or "shell" and similar terms, refer to a layer of metal oxide or semi-metal oxide formed around a particle or particulate matter. The layer or coating need not always be complete or uniform and need not necessarily lead to complete coverage of the particulate matter or particle surface. It is appreciated that upon repetition of the coating steps as the coating process proceeds a more uniform coating and more complete coverage of the particulate matter is obtained.

[0105] The term "dispersion," as used herein, in step (a) of the process refers to a solid dispersion of the particulate matter in the aqueous medium. Step (a) of the process can further comprise reducing the particle size of the particulate matter to the desired particle size, for example, by milling or homogenization.

[0106] The core (i.e., solid, BPO particulate matter) can be of any shape, for example, rod-like, plate-like, ellipsoidal, cubic, spherical shape, combinations thereof and the like.

[0107] Reference to the size of particles will be made through their D_{90}, which means that about 90% of the particles have the stated dimension or less (measured by volume). Thus, for example, for spherical particles stated to have a diameter of about 10 micrometer ("microns"), this means that the particles have a D_{90} of about 10 microns. The D_{90} can be measured by laser diffraction. For particles having a shape other than spheres, the D_{90} refers to the mean average of the diameter of a plurality of particles.

[0108] In the case of cores having a spherical shape, the D_{90} can be in the range of from about 0.3 to 90 microns, in some embodiments from about 0.3 to about 50 microns, in some other embodiments from about 1 to about 50 microns, in some further embodiments from about 5 to about 30 microns. As used herein, the phrase "D_{90} can be in the range of from about 0.3 microns to about 90 microns" means about 90% by volume of the particles (in this case the particle's core) can be less than or equal to a value in the range of from about 0.3 microns to about 90 microns.

[0109] For generally cubic-shaped cores or cores having a shape resembling that of a cube, the mean size of a side can be in the range of from about 0.3 to about 80 microns, in some embodiments from about 0.3 to about 40 microns, in some further embodiments from about 0.8 to about 40 microns, in some further embodiments from about 4 to about 15 microns.

[0110] For rod-like shaped, ellipsoidal-shaped and plate-like shaped cores, the largest dimension (that of the longest axis) is typically in the range of from about 10 to about 100 microns, in some embodiments from about 15 to about 50 microns; and the smallest dimension is typically in the range of from about 0.5 to about 20 microns, in some further embodiments from about 2 to about 10 microns.

[0111] As used herein, unless otherwise indicated, the term "particle" refers to the metal oxide or semi-metal oxide coated particulate matter.

[0112] It is appreciated that some of the particles obtained by the process can at times be formed from two or more original particles of the solid BPO particulate and can accordingly include at times more than one core, such cores being separated from each other by a metal oxide region.

[0113] The weight of the solid BPO particulate (core material) based on the total weight of the particle can be in the range of from about 99% w/w to about 50% w/w, in some embodiments in the range of from about 97% w/w to about 50% w/w. The core material can be in a crystalline form, amorphous form, or combination thereof. The core material can be a cosmetic, pharmaceutical or an agrochemical active ingredient.

Exemplary Embodiments

[0114] BPO-containing compositions were prepared following the various preparation methods described in U.S. Application Publication Nos. 2010/0016443, 2017/0281571 and 2018/0147165 and U.S. Pat. No. 9,687,465, the contents of which are incorporated herein, by reference, in their entirety.

[0115] Description:

[0116] A randomized, double-blind, multi-center, parallel group, active- and vehicle-controlled study of encapsulated 5% benzoyl peroxide cream (E-BPO) and vehicle cream was performed to assess the efficacy and safety of E-BPO compared to vehicle. Study duration was 12 weeks and included approximately 350 male and female patients afflicted with papulopustular rosacea. Patients were at least 18 years of age.

[0117] Patients were admitted into the study after meeting all inclusion/exclusion criteria, including a clinical diagnosis of rosacea. Subjects with moderate to severe rosacea who were appropriate for systemic treatment were counseled regarding their treatment options by the Principal Investigator. At each visit, a 5-point IGA scale of rosacea and inflammatory lesion counts were performed and recorded.

[0118] Dosing:

[0119] Patients were randomly organized in a 2:1 ratio to the study product or vehicle treatment group, respectively. Patients applied the study product once daily for 12 weeks on the face in a thin layer to provide even distribution.

[0120] Clinical and Safety Evaluations were performed at Baseline and Weeks 2, 4, 8 and 12.

[0121] Evaluation of Erythema:

[0122] Erythema is defined as redness of the skin. Erythema was scored on a scale of 0 (none) to 3 (severe) at all visits.

[0123] The percentage of patients with no erythema at baseline with 5% E-BPO and vehicle cream at Baseline and about 2 weeks is shown in Tables 1A and 1B below. As seen from these results, the percentage of patients with no erythema symptoms does not increase after treatment with 5% E-BPO for two weeks.

TABLE 1A

		Example 1A (5% E-BPO)	Comparative Example 1A (vehicle alone)
Baseline (N = 243 for 5% E-BPO; N = 118 for vehicle)	Percentage of Patients with No Erythema Symptoms	0.4	0.0
Week 2 (N = 221 for 5% E-BPO; N = 107 for vehicle)	Percentage of Patients with No Erythema Symptoms	0.4	0.0
	Change from baseline	0.0	0.0
	Percentage change from baseline	0.0	0.0

TABLE 1B

		Example 1B (5% E-BPO)	Comparative Example 1B (vehicle alone)
Baseline (N = 243 for 5% E-BPO; N = 118 for vehicle)	Percentage of Patients with No Erythema Symptoms	0.4	0.0
Week 2 (N = 221 for 5% E-BPO; N = 107 for vehicle)	Percentage of Patients with No Erythema Symptoms	1.2	0.0
	Change from baseline	0.8	0.0
	Percentage change from baseline	20	0.0

[0124] The Rosacea Erythema Assessment Scale for patient groups treated with 5% E-BPO and vehicle cream at Baseline and about 12 weeks is shown in Tables 2A and 2B below. As seen from these results, a percentage decrease of about 60% is observed in a population exhibiting moderate to severe erythema symptoms when measured at about 12 weeks after initial treatment of the population with the pharmaceutical composition. This observed decrease in erythema symptoms is at least about 10% to about 30% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone. These results are shown in FIGS. **1**A and **1**B.

TABLE 2A

		Example 1A (5% E-BPO)	Comparative Example 1A (vehicle alone)
Baseline (N = 243 for 5% E-BPO; N = 118 for vehicle)	Percentage of Patients with Moderate and Severe Erythema	85.6	87.2
Week 12 (N = 221 for 5% E-BPO; N = 107 for vehicle)	Percentage of Patients with Moderate and Severe Erythema	33.0	57.9
	Change from baseline	−52.6	−29.3
	Percentage change from baseline	−61.4	−33.6

TABLE 2B

		Example 1B (5% E-BPO)	Comparative Example 1B (vehicle alone)
Baseline (N = 250 for 5% E-BPO; N = 122 for vehicle)	Percentage of Patients with Moderate and Severe Erythema	94.0	95.9
Week 12 (N = 235 for 5% E-BPO; N = 113 for vehicle)	Percentage of Patients with Moderate and Severe Erythema	38.7	48.7
	Change from baseline	−55.3	−47.2
	Percentage change from baseline	−58.8	−49.2

[0125] The above-discussed results demonstrate the unexpected superiority of the benzoyl peroxide composition described in this application in the treatment of severe rosacea in patients in need of such treatment.

[0126] Although the exemplary embodiments of the present disclosure have been described in detail with reference to the accompanying examples and drawings, the present disclosure is not limited thereto and can be embodied in many different forms without departing from the technical concept of the present disclosure. Therefore, the exemplary embodiments of the present disclosure are provided for illustrative purposes only and are not intended to limit the technical concept of the present disclosure. The protective scope of the present disclosure should be construed based on any appended claims and combinations thereof, and all the technical concepts in the equivalent scope thereof should be construed as falling within the scope of the present disclosure. As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the exemplary embodiments disclosed herein. It is intended that the specification be considered exemplary only, with the scope and spirit of the described subject matter being indicated by the claims.

What is claimed is:

1. A regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 2.5% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 12 weeks, to achieve a percentage decrease of about 60% in a population exhibiting moderate to severe erythema symptoms when measured at about 12 weeks after initial treatment of the population with the pharmaceutical composition, and wherein the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 10% to about 30% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

2. The regimen of claim **1**, wherein the percentage decrease in the population exhibiting erythema symptoms after treatment with pharmaceutical composition is at least about 18% higher than a corresponding decrease in the population exhibiting erythema symptoms after treatment with a vehicle alone.

3. The regimen of claim **1**, wherein the benzoyl peroxide is the sole active ingredient administered to the subject during the duration of the regimen.

4. The regimen of claim **1**, wherein the pharmaceutical composition comprises about 5% w/w of the benzoyl peroxide.

5. The regimen of claim **1**, wherein the benzoyl peroxide is in a solid, solution or suspension form.

6. The regimen of claim **1**, wherein the regimen is a first line therapy for the treatment of moderate to severe rosacea.

7. The regimen of claim **1**, wherein the moderate to severe rosacea is any of erythematotelengietatic rosacea, papulopustular rosacea, phymatous rosacea or ocular rosacea.

8. The regimen of claim **1**, wherein said pharmaceutical composition is a cream or an emulsion.

9. The regimen of claim **1**, wherein said pharmaceutical composition is an extended-release formulation.

10. The regimen of claim **9**, wherein an extended-release effect from the extended-release formulation is obtained by encapsulation, microencapsulation, microspheres or coating.

11. The regimen of claim **10**, wherein the benzoyl peroxide is encapsulated or microencapsulated.

12. The regimen of claim **10**, wherein the benzoyl peroxide is included in a microsphere or a coating.

13. A regimen for the therapeutic treatment of moderate to severe erythema symptoms in rosacea patients, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 2.5% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, and wherein after about 2 weeks of treatment with the pharmaceutical composition there is no increase in erythema symptoms.

14. The regimen of claim **13**, wherein the number of patients with no erythema symptoms does not increase after treatment for about 2 weeks with the pharmaceutical composition.

15. The regimen of claim **13**, wherein the pharmaceutical composition comprises about 5% w/w of the benzoyl peroxide.

16. The regimen of claim **13**, wherein the benzoyl peroxide is in a solid, solution or suspension form.

17. The regimen of claim **13**, wherein the regimen is a first line therapy for the treatment of moderate to severe rosacea.

18. The regimen of claim **13**, wherein the moderate to severe rosacea is any of erythematotelengietatic rosacea, papulopustular rosacea, phymatous rosacea or ocular rosacea.

19. The regimen of claim **13**, wherein said pharmaceutical composition is a cream or an emulsion.

20. The regimen of claim **13**, wherein said pharmaceutical composition is an extended-release formulation.

21. The regimen of claim **20**, wherein an extended-release effect from the extended-release formulation is obtained by encapsulation, microencapsulation, microspheres or coating.

22. The regimen of claim **21**, wherein the benzoyl peroxide is encapsulated or microencapsulated.

23. The regimen of claim **21**, wherein the benzoyl peroxide is included in a microsphere or a coating.

* * * * *