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# DESCRIPTION

## BACKGROUND OF THE INVENTION

**[0001]** Parabens are esters of para-hydroxybenzoic acid. They are used primarily for their bactericidal and fungicidal properties. Examples of parabens include methylparaben, ethylparaben, propylparaben, butylparaben, isobutylparaben, isopropylparaben, benzylparaben and their salts. Because of their low costs, long history of safe use and the inefficacy of natural alternatives, parabens are widely used as preservatives in the cosmetic and pharmaceutical industries. See Darbre et al., 24 J. Appl. Toxicol. 5-13 (2004) and references therein.

**[0002]** Carbomer is a generic name of Carbopol®, a trademarked product from Lubrizol. Carbomer and Carbopol® are used interchangeably in the present application, referring to a synthetic polymer of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. It can be a homopolymer of acrylic acid, cross-linked with an allyl ether pentaerythritol, allyl ether of sucrose, or allyl ether of propylene. Carbomers have been used as vehicles for drug delivery. They have a long history of safe and effective use in topical gels, creams, lotions, and ointments, as supported by extensive toxicology studies. They have been shown to have extremely low irritancy properties and are non-sensitizing with repeat usage. Carbomers or carbomer copolymers have been used in topical formulations, e.g., for thickening, emulsifying or suspending.

**[0003]** Brimonidine is a selective alpha-2-adrenergic agonist. It has been used as either monotherapy or as adjunctive therapy to lower intraocular pressure (IOP) in the treatment of glaucoma and ocular hypertension (OHT) since its approval in 1996. Brimonidine has also been found to be useful in treating various skin disorders, such as rosacea, erythema caused by rosacea, see, e.g., U.S. Ser. No. 10/853,585 to DeJovin et al.; U.S. Ser. No. 10/626,037 to Scherer; U.S. Ser. No. 12/193,098 to Theobald et al.; telangiectasias, see, e.g., U.S. Patent Application Publication No. 2006/0264515. Topical gel compositions comprising brimonidine, carbomer and paraben(s) for the treatment of skin disorders have been described, see for example, U.S. Ser. No. 10/853,585 to DeJovin et al.; U.S. Ser. No. 12/193,098 (Publication No. US 2009/0061020) to Theobald et al., etc. In particular, U.S. Patent Application Publication No. 2009/0061020 and WO 2009/03223 A1 describe the use of a topical composition comprising:

0.18% (w/w) brimonidine tartrate;

0.3% methylparaben;

0.4 (w/w) of an additional preservative, namely phenoxyethanol;

1.25% (w/w) carbomer 934P;

5.5% (w/w) glycerin;

5.5% (w/w) propylene glycol; and  
0.625% (w/w) of 10% titanium dioxide.

**[0004]** Crystalline particles of methylparaben have been unexpectedly observed in some brimonidine topical gel formulations and placebo formulations containing carbomer and methylparaben.

**[0005]** There is a need for a topical gel composition containing carbomer and methylparaben that is substantially free of paraben crystalline particles and meets the antimicrobial requirement over an extended period of storage. Such compositions and related methods and products are described in the present application.

#### **BRIEF SUMMARY OF THE INVENTION**

**[0006]** In one general aspect, the present invention relates to a topical gel composition comprising:

0.05 to 5% (w/w) brimonidine or brimonidine tartrate;  
0.05 to 0.20% (w/w) of the preservative, methylparaben;  
0.3 to 0.5% (w/w) of the further preservative, phenoxyethanol;  
0.80 to 1.50% (w/w) carbomer; and  
9.0 to 13.0% (w/w) total polyol;

wherein the topical gel composition has a pH of 4.5 to 7.5; and wherein when the concentration of methylparaben is greater than 0.15% (w/w), the concentration of carbomer is less than 1.25% (w/w).

**[0007]** In a specific embodiment of the present invention, the topical gel composition comprises:

0.01 to 5% (w/w) brimonidine or brimonidine tartrate.

**[0008]** In a preferred embodiment of the present invention, the topical gel composition comprises:

0.1 to 0.6% (w/w) brimonidine tartrate;

0.05 to 0.15% (w/w) methylparaben;

0.80 to 1.50% (w/w) carbomer ;

4.5 to 6.5% (w/w) propylene glycol;

4.5 to 6.5% (w/w) glycerol; and

purified water;

wherein the pH of the topical gel composition is adjusted to a pH of 5.0 to 6.5 by an adequate amount of sodium hydroxide aqueous solution.

**[0009]** In another general aspect, the present invention relates to a topical gel composition according to an embodiment of the present invention for use in treating or preventing a skin disorder in a subject, wherein the composition is to be topically administered to a skin area of the subject which is, or is prone to be, affected by the skin disorder.

**[0010]** Other aspects, features and advantages of the invention will be apparent from the following disclosure, including the detailed description of the invention and its preferred embodiments and the appended claims.

#### **DETAILED DESCRIPTION OF THE INVENTION**

**[0011]** Discussion of documents, acts, materials, devices, articles, or the like which have been included in the present specification is for the purpose of providing context for the present invention. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to any inventions disclosed or claimed.

**[0012]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification. It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise.

**[0013]** As used herein, "erythema or a symptom associated therewith" is intended to encompass any type or classification of redness of skin caused by hyperemia or congestion of the capillaries in the lower layers of the skin, and any symptom associated therewith. The term "erythema or a symptom associated therewith" encompasses skin redness or rash resulting from any causes. For example, it can be caused by skin injury, surgery and other procedures on the skin, infection, inflammation, emotion, exercise, heat (erythema ab igne), cold, photosensitivity, radiation therapy, allergy, hot flush diseases, medications, etc. Examples of "erythema or a symptom associated therewith" include, but are not limited to, photosensitivity,

erythema multiforme, and erythema nodosum, and their associated symptoms. Photosensitivity is caused by a reaction to sunlight, which often occurs when some factors, such as an infection or a medication, increase the sensitivity to ultraviolet radiation. However, photosensitivity can also occur without any increased sensitivity to ultraviolet radiation. Erythema multiforme is characterized by raised spots or other lesions on the skin, which are usually caused by a reaction to medications, infections, or illness. Most erythema multiforme is associated with herpes simplex or mycoplasma infections. Erythema nodosum is a form of erythema that is accompanied by tender lumps, usually on the legs below the knees, and may be caused by certain medications or diseases.

**[0014]** In one particular embodiment of the present invention, the term "erythema or a symptom associated therewith" includes erythema of rosacea, i.e., erythema or a symptom associated therewith in a patient with rosacea. Rosacea is an inflammatory skin disorder that generally affects the cheeks, nose, chin, and forehead of a patient. The major symptom of rosacea is erythema, i.e., the abnormal redness of the skin.

**[0015]** The term "erythema or a symptom associated therewith" encompasses different degrees or grades of erythema or a symptom associated therewith, from mild to severe.

**[0016]** In view of the present disclosure, a skin area that is affected by erythema or that is prone to be affected by erythema can be identified using any diagnostic signs or means known in the art, and can be treated with topical gel compositions according to embodiments of the present invention.

**[0017]** As used herein, "telangiectasia or a symptom associated therewith" refers to a visible, permanent abnormal dilation of blood vessels, such as arterioles and venules. A visible blood vessel is a blood vessel visually discernable as a line to an observer without the aid of magnifying equipment (other than spectacles normally used by the observer). In various aspects, a telangiectatic blood vessel can have a diameter of at least about 0.5 mm. Telangiectasias can be associated with numerous conditions, syndromes, diseases, and disorders. For example, a facial telangiectasia can be associated with age, sun exposure, and alcohol use. Other diseases, disorders, conditions, and syndromes associated with telangiectasias include, in non-limiting example, scleroderma, hereditary hemorrhagic telangiectasia (Osler-Rendu syndrome), ataxia-telangiectasia, spider angioma, cutis marmorata telangiectasia congenita, Bloom syndrome, Klippel-Trenaunay-Weber syndrome, Sturge-Weber disease, xeroderma pigmentosa, nevus flammeus, generalized essential telangiectasias (GET), angioma serpiginosum, spider naevi, CREST syndrome, basal cell carcinoma, and unilateral nevoid telangiectasia.

**[0018]** In one particular embodiment of the present invention, the term "telangiectasia or a symptom associated therewith" includes telangiectasia associated with rosacea, i.e., telangiectasia or a symptom associated therewith in a patient with rosacea.

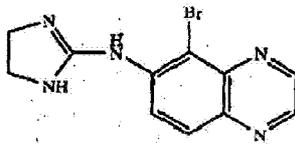
**[0019]** In another particular embodiment of the present invention, the term "telangiectasia or a

symptom associated therewith" includes sun-induced/photodamage telangiectasia.

**[0020]** The term "telangiectasia or a symptom associated therewith" encompasses different degrees or grades of telangiectasia or symptoms associated therewith, from mild to severe.

**[0021]** In view of the present disclosure, a skin area that is affected by telangiectasia or that is prone to be affected by telangiectasia can be identified using any diagnostic signs or means known in the art, and can be treated with topical gel compositions according to embodiments of the present invention.

**[0022]** As used herein, the term "brimonidine" refers to the compound (5-bromo-quinoxalin-6-yl)-(4,5-dihydro-1H-imidazol-2-yl)-amine having the structure of Formula (I):



Formula (I)

and any pharmaceutically acceptable salt of the compound, such as brimonidine tartrate.

**[0023]** The phrase "pharmaceutically acceptable salt(s)," as used herein, means those salts of a compound of interest that are safe and effective for topical use in mammals and that possess the desired biological activity. Pharmaceutically acceptable salts include salts of acidic or basic groups present in the specified compounds. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts see Berge et al., 66 J. Pharm. Sci. 1-19 (1977).

**[0024]** As used herein, the term "hydrate" means a compound of interest, or a pharmaceutically acceptable salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound to it by non-covalent intermolecular forces.

**[0025]** The term "topical gel composition" or "topical gel formulation," as used herein, means any gel formulation or composition which is pharmaceutically and/or cosmetically acceptable for topical delivery of the specified compound(s).

**[0026]** As used herein, the term "composition" is intended to encompass a product comprising the specified ingredient in the specified amount, as well as any product which results, directly or indirectly, from combinations of the specified ingredient in the specified amount.

**[0027]** As used herein, the term "subject" means any animal, preferably a mammal, most preferably a human, to whom will be or has been administered compounds or topical formulations according to embodiments of the invention. The term "mammal" as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys, humans, etc., more preferably a human. Preferably, a subject is in need of, or has been the object of observation or experiment of, treatment or prevention of a skin disorder, such as rosacea, erythema of rosacea, telangiectasia, psoriasis, purpura, erythema of acne, eczema, non-rosacea-related inflammation of the skin, flushing, skin sagging, creasing and/or wrinkling, or a symptom associated therewith.

**[0028]** In one aspect, "treatment" or "treating" refers to an amelioration, prophylaxis, or reversal of a disease or disorder, or of at least one discernible symptom thereof. In another aspect, "treatment" or "treating" refers to an amelioration, prophylaxis, or reversal of at least one measurable physical parameter related to the disease or disorder being treated, not necessarily discernible in or by the mammal. In yet another aspect, "treatment" or "treating" refers to inhibiting or slowing the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder.

**[0029]** In certain situations, compounds of interest are administered as a preventative measure. As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. In a preferred mode of the embodiment, the specified compounds are to be administered as a preventative measure to a subject having a predisposition to a disease or disorder even though symptoms of the disease or disorder are absent or minimal.

**[0030]** As an aspect of the realization of the present invention, methylparaben crystalline particles have been observed in brimonidine topical gel formulations containing 0.2% (w/w) or more methylparaben, particularly in batch sizes of 300 g to 250 kg. See Example 1 below. This observation is surprising in view of the solubility of methylparaben. According to a Material Safety Data Sheet (MSDS) of methylparaben, the solubility of methylparaben in water is about 0.25% (w/w) at 20 °C or about 0.30% (w/w) at 25°C. The solubility of methylparaben in propylene glycol is 1 in 5 at 25 °C, the solubility of methylparaben in warm glycerol is about 1.4%, and see: MSDS, Chemicals & Laboratory Equipment, Science Lab.com, World Wide Web: [sciencelab.com/msds.php?msdsId=9926083](http://sciencelab.com/msds.php?msdsId=9926083). Further, according to *Handbook of Pharmaceutical Excipients* (supra), the solubility of methylparaben in propylene glycol is 1 in 5 at 25 °C.

**[0031]** In view of methylparaben's solubility in polyols and water, it would have been reasonably expected that 0.30% (w/w) or less methylparaben would remain completely soluble in a topical gel composition comprising about 4.5 to 6.5% (w/w) of a first polyol in which methylparaben is substantially soluble, about 4.5 to 6.5% (w/w) of a second polyol, and about

90% (w/w) or less water. The detection of methylparaben crystalline particles in the composition is completely unexpected. Not wishing to be bound by theory, the methylparaben crystalline particles observed in the brimonidine topical gel and placebo compositions may have been caused by one or more reasons, such as recrystallization of methylparaben during the manufacturing process, or recrystallization of methylparaben during storage resulting from excipient-excipient interaction. Without the surprising observation made herein above, one would not have reasonably expected the existence of methylparaben crystals in the topical gel compositions, let alone to develop an improved topical gel formulation free of the crystals.

**[0032]** The present invention relates to an improved topical gel composition that is substantially free of crystalline particles and has microbiological quality over an extended period of storage. The improved topical gel composition according to the present invention comprises

0.05 to 5% (w/w) brimonidine or brimonidine tartrate;

0.05 to 0.20% (w/w) of the preservative, methylparaben;

0.3 to 0.5% (w/w) of the further preservative, phenoxyethanol;

0.80 to 1.50% (w/w) carbomer; and

9.0% to 13.0% (w/w) total polyol;

wherein the topical gel composition has a pH of 4.5 to 7.5; and

wherein when the concentration of methylparaben is greater than 0.15% (w/w), the concentration of carbomer is less than 1.25% (w/w).

**[0033]** According to the present invention, the amount of methylparaben in the composition is about 0.05%, 0.075%, 0.10%, 0.125%, 0.15%, or 0.20% (w/w).

**[0034]** According to embodiments of the present invention, the amount of phenoxyethanol in the composition is, or is greater than 0.3%, 0.35%, 0.4%, 0.45%, or is 0.5% (w/w).

**[0035]** According to the present invention, the carbomer is a synthetic polymer of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. It can be a homopolymer of acrylic acid, cross-linked with an allyl ether pentaerythritol, allyl ether of sucrose, or allyl ether of propylene. Examples of carbomers that can be used in the present invention include, but are not limited to, carbomer 910, 934P, 940, 941, 1342, Carbopol® 974P (carbomer 974P), and Carbopol® 980 (carbomer 980).

**[0036]** Preferably, the carbomer is carbomer 934P, carbomer 974P, or carbomer 980.

**[0037]** According to the present invention, the amount of the carbomer in the composition is about 0.8%, 0.85%, 0.95%, 1.05%, 1.15%, 1.25%, 1.35%, 1.45%, or 1.5% (w/w).

**[0038]** Polyol gel formulations with various ingredients solubilized therein have been used to minimize irritation when applied to the skin of a subject, while ensuring bioavailability of the active agent in the formulation. See Other III et al., "Gels and Jellies," pp. 1327-1344 of Encyclopedia of Pharmaceutical Technology, vol. 3 (ed. by Swarbrick et al., pub. by Marcel Dekker, Inc., 2002); or Pena, "Gel Dosage Forms: Theory, Formulation, and Processing," pp. 381-388 of Topical Drug Delivery Formulations, (ed. by Osborne et al., pub. by Marcel Dekker, Inc., 1990). Polyols in gel formulations can serve one or more functions, such as solubilizing agents, moisturizers, emollients, skin humectant, skin-penetration agents, etc. Suitable polyols that can be used in embodiments of the present invention include, but are not limited to, glycerine, propylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, and liquid polyethylene glycols, such as polyethylene glycol 200 to 600, and glycerol.

**[0039]** According to the present invention, the amount of the total polyols in the composition is about 9.0% to 13.0% (w/w), for example about 9.0%, 9.5%, 10.0%, 10.5%, 11.0%, 11.5%, 12.0%, 12.5%, or 13.0% (w/w).

**[0040]** In an aspect of the present invention, the topical gel composition comprises at least a first polyol in which the methylparaben is substantially soluble.

**[0041]** Preferably, the topical gel composition comprises the first polyol and a second polyol, such as propylene glycol and glycerine, respectively.

**[0042]** According to the present invention, the amount of each of the first and second polyols in the composition is independently about 4.5% to 6.5% (w/w), for example 4.5%, 5.0%, 5.5%, 6.0%, or 6.5% (w/w).

**[0043]** In a preferred embodiment, a topical gel composition according to embodiments of the invention further comprises a water dispersible form of titanium dioxide ( $\text{TiO}_2$ ), preferably at an amount that is sufficient to mask the color of brimonidine or another colored ingredient in the formulation, but would not cause irritation to the skin.  $\text{TiO}_2$  may cause mild irritation and reddening to the eyes, thus eye contact with the  $\text{TiO}_2$ -containing topically administrable composition should be avoided. Titanium dioxide imparts a whiteness to the topically administrable composition and helps to increase the opacity and reduce the transparency of the composition. Titanium dioxide absorbs, reflects, or scatters light (including ultraviolet radiation in light), which can help protect products from deterioration. Titanium dioxide can also be used as a sunscreen to protect the user from the harmful effects of ultraviolet radiation that is part of sunlight.

**[0044]** According to the present invention, the amount of water dispersible form of titanium dioxide in the composition is about 0.04%, 0.0425%, 0.0525%, 0.0625%, 0.0725%, or 0.08% (w/w).

**[0045]** As noted herein above, a topical gel formulation according to the present invention further comprises an active pharmaceutical ingredient, namely the alpha adrenergic receptor

agonist brimonidine or the pharmaceutically acceptable tartrate salt thereof, that is effective to prevent or treat a skin disorder.

**[0046]** Alpha adrenergic receptor agonists are well known in the art and may or may not show selectivity for either the alpha-1 or alpha-2 adrenergic receptors. The alpha adrenergic receptor agonist, brimonidine, is a selective alpha-2 adrenergic receptor agonist.

**[0047]** In an aspect of the present invention, the active pharmaceutical ingredient comprises 0.01 to 5% (w/w) brimonidine. The active pharmaceutical ingredient can optionally include one or more pharmaceutically active ingredients in addition to brimonidine, including, but not limited to, medications used to treat the skin disorder or the underlying disease that causes the skin disorder, antihistamines to control itching, antibiotics, corticosteroids, intravenous immunoglobulins, acetaminophen, etc.

**[0048]** In a preferred embodiment, the brimonidine is brimonidine tartrate.

**[0049]** According to the present invention, the amount of brimonidine in the topical gel composition is about 0.05% to 0.1%, 0.1% to 0.4%, 0.4% to 0.7%, 0.7% to 1%, 1% to 2%, 2% to 3%, 3% to 4%, or 4% to 5% (w/w). Preferably, the amount of brimonidine tartrate in the composition is about 0.1 to 0.6% (w/w).

**[0050]** In a preferred embodiment of the present invention, a topical gel composition comprises:

0.1 to 0.6% (w/w) brimonidine tartrate;

0.05 to 0.15% (w/w) methylparaben;

0.3 to 0.5% (w/w) phenoxyethanol;

0.80 to 1.50% (w/w) carbomer;

4.5 to 6.5% (w/w) propylene glycol;

4.5 to 6.5% (w/w) glycerol; and

purified water;

wherein the pH of the topical gel composition is adjusted to 5.0 to 6.5 by an adequate amount of sodium hydroxide aqueous solution.

**[0051]** According to the present invention, the topical gel composition comprises greater than 0.3% (w/w) phenoxyethanol as the further preservative when 0.15% (w/w) or less methylparaben is used in the formulation.

**[0052]** A topical gel composition according to the present invention can comprise additional pharmaceutically acceptable excipients, such as those listed in Remington: The Science and

Practice of Pharmacy, 866-885 (Alfonso R. Gennaro ed., 19th ed., 1995); Ghosh, T. K. et al., Transdermal and Topical Drug Delivery Systems (1997). Examples of the additional excipients include, but are not limited to, protectives, adsorbents, antioxidants, local anesthetics, buffering agents, surfactants, flavorants, fragrances, dyes, etc.

**[0053]** Suitable protective agents and/or cosmetic agents, and adsorbents can include, but are not limited to, dusting powders, zinc stearate, collodion, dimethicone, silicones, zinc carbonate, aloe vera gel and other aloe products, vitamin E oil, allantoin, petrolatum, titanium dioxide, and zinc oxide.

**[0054]** Suitable antioxidants can include, but are not limited to, ascorbic acid and its esters, sodium bisulfite, butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, and chelating agents like EDTA and citric acid.

**[0055]** Suitable buffering agents can include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers, lactic acid buffers, sodium buffer, and borate buffers.

**[0056]** A topical gel composition according to the present invention can further include local anesthetics and analgesics, such as camphor, menthol, lidocaine, dibucaine, and pramoxine; antifungals, such as ciclopirox, chloroxylenol, triacetin, sulconazole, nystatin, undecylenic acid, tolnaftate, miconazole, clotrimazole, oxiconazole, griseofulvin, econazole, ketoconazole, and amphotericin B.

**[0057]** A topical gel composition according to the present invention can further include one or more antiseptics, such as iodine, povidine-iodine, benzalkonium chloride, benzoic acid, nitrofurazine, benzoyl peroxide, hydrogen peroxide, hexachlorophene, phenol, resorcinol, and cetylpyridinium chloride.

**[0058]** The topical gel composition according to the present invention can be prepared by mixing the ingredients of the composition according to known methods in the art, for example methods provided by standard reference texts such as: Remington: The Science and Practice of Pharmacy, 1577-1591, 1672-1673, 866-885 (Alfonso R. Gennaro ed., 19th ed., 1995); Ghosh, T. K. et al., Transdermal And Topical Drug Delivery Systems (1997).

**[0059]** The pH of the topical gel formulations of the invention are within the physiologically acceptable pH range of about 4.5 to about 7.5, more preferably, of about 5.0 to about 6.5, such as a pH of about 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, 5.5, 5.55, 5.6, 5.65, 5.7, 5.75, 5.8, 5.85, 5.9, 5.95, 6.1, 6.15, 6.2, 6.25, 6.3, 6.35, 6.4, 6.45, or 6.5. To stabilize the pH, preferably, an effective amount of a buffer is included. Acids or bases can be used to adjust the pH as needed.

**[0060]** In one general aspect, the present invention further relates to a topical gel composition according to any of the embodiments of the present invention as mentioned above, for its use in the treatment or the prevention of a skin disorder in a subject, wherein the topical gel

composition is to be topically administered to a skin area of the subject which is, or is prone to be, affected by the skin disorder, such as rosacea, erythema of rosacea, telangiectasias, psoriasis, purpura, erythema of acne, ezama, non-rosaced-related inflammations of skin, flushing, skin sagging, creasing and/or wrinkling, or a symptom associated therewith.

**[0061]** The relevant disclosures, e.g., on using brimonidine to treat the one or more skin disorders are set forth in U.S. Ser. No. 10/853,585 to DeJovin et al.; U.S. Ser. No. 10/626,037 to Scherer; U.S. Ser. No. 10/607,439 to Gil et al.; U.S. Ser. No. 10/763,807 to Shanler et al.; U.S. Ser. No. 12/193,098 to Theobald et al.; U.S. Patent Application Publication No. 2006/0264515 to DeJovin et al.; U. S. Ser. No. 12/621,942 to DeJovin et al.; U.S. Patent Application Publication No. 2005/0020600 to Scherer; and U.S. Patent Application Publication No. 2009/0130027 to Shanler et al..

**[0062]** As mentioned herein above, in an aspect of the present invention, the topically administrable composition comprises about 0.1% to 0.6% (w/w), such as about 0.1%, about 0.15%, about 0.18%, about 0.2%, about 0.25%, about 0.3%, about 0.35%, about 0.4%, about 0.45%, about 0.5%, about 0.55%, or about 0.6% by weight of brimonidine tartrate.

**[0063]** To treat or prevent a skin disorder, in view of the present disclosure, the topical gel compositions of the invention can be topically applied directly to the affected area in any conventional manner known in the art, e.g. by dropper, applicator stick, or cotton swab, as a mist via an aerosol applicator, via an intradermal or transdermal patch, or by simply spreading a formulation of the invention onto the affected area with fingers, a sponge, a pad, or wipes. Generally, the amount of a topical formulation of the invention applied to the affected skin area ranges from about 0.0001 g/cm<sup>2</sup> of skin surface area to about 0.05 g/cm<sup>2</sup>, preferably 0.002 g/cm<sup>2</sup> to about 0.005 g/cm<sup>2</sup> of skin surface area. Typically, one to four applications per day are recommended during the term of treatment.

**[0064]** Compositions of the present invention can be used in conjunction with one or more other treatments and medications for the skin disorder, such as the medications used to treat the underlying disease that causes the skin disorder, antihistamines to control itching, antibiotics, corticosteroids, intravenous immunoglobulins, acetaminophen, etc.

**[0065]** The other medicament or treatment can be administered to the subject simultaneously with, or in a sequence and within a time interval of, the administration of brimonidine, such that the active ingredients or agents can act together to treat or prevent the skin disorder. For example, the other medicament or treatment and brimonidine can be administered in the same or separate formulations at the same or different times.

**[0066]** Any suitable route of administration can be employed to deliver the additional treatment or medication including, but not limited to, oral, intraoral, rectal, parenteral, topical, epicutaneous, transdermal, subcutaneous, intramuscular, intranasal, sublingual, buccal, intradural, intraocular, intrarespiratory, or nasal inhalation.

[0067] This invention will be better understood by reference to the non-limiting examples that follow, but those skilled in the art will readily appreciate that the examples are only illustrative of the invention as described more fully in the claims which follow thereafter.

**Example 1 (not within scope of appended claims)**

**Observation of Methylparaben Crystalline Particles in Topical Gel Compositions**

[0068] Crystalline particles were first observed visually in a sampling of 7 tubes of a batch of brimonidine topical gel composition. These particles were isolated. The identity of the particles was analyzed by several analytical methods, such as HPLC test for identification by comparison of the retention time against standards, differential scanning calorimetry (DSC) for determination of melting point, NMR for a structural identification (by  $^1\text{H}$  and  $^{13}\text{C}$ ), mass/ mass with UV detector and QTOF to separate and identify the different masses, etc. Based on these analyses, it has been concluded that the observed crystals are crystals of methylparaben (hereinafter abbreviated as POBM or MPOB), which is a preservative used in the composition. According to the process used for manufacturing the batch, methylparaben was first dissolved in propylene glycol at  $50^\circ\text{C}$  ( $122\text{-}140^\circ\text{F}$ ) in the preservative phase.

[0069] Microscopic observations were performed on additional representative batches of brimonidine topical gel compositions and placebo gel compositions containing 1.25% (w/w) carbomer, POBM and other ingredients. The observations have been done on one tube of each batch, with the microscope AxioLab DRBKT Zeiss no. 023733.01 with a camera ICC Zeiss or the microscope Olympus BX60. The microscopic observations were done at  $5^\circ\text{C}$  and room temperature.

[0070] As shown in Table 1, methylparaben crystalline particles were unpredictably observed in both brimonidine and placebo gel compositions containing 0.2% or 0.3% by weight methylparaben (POBM).

Table 1: Results of microscopic observations of representative batches of gel composition

Date of Manufacturing	Composition	Microscopic Observation	Batch Size	No. Tubes Observed	Date of Observation
	Placebo, 0.3%		130 kg		
April 2008	POBM Placebo, 0.3%	Crystals	130 kg	7	Dec. 2008
April 2008	POBM Placebo, 0.3%	No crystal	300g-2kg	5	Dec. 2008
July 1, 2009	POBM	Crystals		1	Oct. 2009

Date of Manufacturing	Composition	Microscopic Observation	Batch Size	No. Tubes Observed	Date of Observation
August 25, 2009	Placebo, 0.3% POBM	Crystals	300g- 2kg	1	Oct. 2009
	0.03% Brimonidine		200 - 250		
Sept. 2, 2009	0.3% POBM	No crystal	kg 200 - 250	1	Feb. 2010
	0.06% Brimonidine				
Sept. 7, 2009	0.3% POBM	Crystals	kg 200 - 250	1	Feb. 2010
	0.07% Brimonidine				
July 6, 2009	0.3% POBM	Crystals	kg 300g- 2kg	1	Feb. 2010
	0.18% Brimonidine				
Sept 15, 2009	0.3% POBM	Crystals	200- 250	1	Oct. 2009
	0.5% Brimonidine				
July 16, 2009	0.3% POBM	Crystals	kg 200 -250	1	Feb. 2010
	1% Brimonidine 1%				
Sept. 18, 2009	0.3% POBM	No crystal	kg 200 -250	1	Feb. 2010
	2% Brimonidine 2%				
Sept. 29, 2009	0.3% POBM	No crystal	kg 300g- 2kg	1	Feb. 2010
	0.06% Brimonidine				
Sept. 10, 2009	0.3% POBM	Crystals	300g- 2kg	1	Oct. 2009
	1% Brimonidine				
Sept. 17, 2009	0.3% POBM	No crystal	300 g	1	Oct. 2009
	Placebo, 0.2%				
Jan. 12, 2010	POBM 0.18% Brimonidine	Crystals	800g	1	Feb. 4, 2010 Feb. 10,
Dec. 22, 2009	0.2% POBM	No crystal		1	2010

[0071] Assays were conducted to estimate the concentration of methylparaben solubilized in a

batch originally containing 0.3% (w/w) of methylparaben, in which crystalline particles were observed. Centrifugation was performed on the batch to collect crystals at the bottom of the centrifuge tube, thus removing them from the supernatant. The methylparaben concentration in the supernatant was measured and found to be about 0.2% (w/w), which was about 66% of the 0.3% (w/w) in the original formulation. The reduction in the concentration of soluble methylparaben in the composition raises nonconformity issues and may result in poor microbiological quality of the composition over an extended period of storage.

**[0072]** The presence of methylparaben crystalline particles in the topical gel formulations is surprising in view of the solubility of methylparaben. In order to find a solution to avoid the crystallization problem, several hypotheses have been postulated and evaluated to uncover the potential cause and possible solution of the problem.

### **Example 2**

#### **Improved Topical Gel Compositions Free of Methylparaben Crystalline Particles**

**[0073]** Various changes to the formulation and the process of manufacturing the formulation have been made in order to obtain improved topical gel formulations that are free of the observed paraben crystals and have acceptable microbiological quality. For example, methylparaben, also named methyl parahydroxybenzoate (POBM), was replaced with the more water soluble Na POBM, but crystalline particles of Na POBM were still observed at 0.3% (w/w) Na POBM. Addition of 0.1% of EDTA into the formulation resulted in immediate recrystallization of the POBM at 0.3% (w/w) in the formulation, suggesting that the 0.3% (w/w) concentration of POBM may be too high.

**[0074]** Numerous formulations with different ingredients and varying concentrations of the ingredients were made and tested for the presence of the paraben crystals by microscopic observations. The microbiological quality of the formulations was also analyzed by using acceptance-test criteria in preservative-efficacy testing (PET) in the United States Pharmacopeia (USP) and the European Pharmacopoeia (EP).

**[0075]** Based on microscopic observations and PET analyses, it was found that improved topical gel compositions containing an effective amount of brimonidine tartrate, 0.05% to 0.20% (w/w) methylparaben; 0.3% (w/w) or more of the further preservative phenoxyethanol; 0.80 to 1.50% (w/w) carbomer, such as Carbopol®974P NF; 9.0% to 13.0% (w/w) total polyol, such as 4.5 to 6.5% (w/w) of a first polyol, e.g., propylene glycol, 4.5 to 6.5% (w/w) of a second polyol, e.g., glycerol; and one or more other ingredients, such as purified water, titanium dioxide, with a pH of 5.0 to 6.5 adjusted by an adequate amount of sodium hydroxide, were free of methylparaben crystals after an extended period of storage and passed criteria of EP and USP. See Table 2, in which the concentration of carbomer in each of the formulations was 1.25%

(w/w).

Table 2: Results of microscopic observations and PET of topical gel formulations

Batch Size (kg)	Preservative Concentration (w/w)	Period of Storage (weeks)	Microscopic Observation	PET Result
2	0.1% MPOB	21	No crystal	Failed criteria A of EP at 48 hours
	0.3% Phenoxyethanol			
200	0.1% MPOB	24	No crystal	Passed EP and USP
	0.4% Phenoxyethanol			
2	0.125% MPOB	12	No crystal	Passed EP and USP
	0.4% Phenoxyethanol			
200	0.125% MPOB	7	No crystal	Passed EP and USP
	0.4% Phenoxyethanol			

[0076] It was further discovered that when the amount of methylparaben was more than 0.15% (w/w), decreasing the amount of carbomer reduced the formation of methylparaben crystals. See, for example, Table 3.

Table 3: Results of microscopic observation of gel compositions

Batch Size	Composition	Microscopic Observation
300G	POBM : 0.2	Crystals after one month storage at RT
	Phenoxyethanol : 0.3	
	Carbopol® 980 : 1.25**	
300G	POBM : 0.2	No crystal observed after one month storage at RT
	Phenoxyethanol : 0.3	
	Carbopol® 980 : 0.8	
** not within scope of appended claims		

[0077] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the scope of the present invention as defined by the appended claims.

## REFERENCES CITED IN THE DESCRIPTION

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## PATENTKRAV

1. Topisk gelsammensætning, der omfatter:
  - 0,05 til 5 % (vægt/vægt) brimonidin eller brimonidintartrat;
  - 0,05 til 0,20 % (vægt/vægt) af konserveringsmidlet, methylparaben;
  - 5 0,3 til 0,5 % (vægt/vægt) af det yderligere konserveringsmiddel, phenoxyethanol;
  - 0,80 til 1,50 % (vægt/vægt) af en carbomer og
  - 9,0 til 13,0 % (vægt/vægt) total polyol;
  - hvor den topiske gelsammensætning har et pH på 4,5 til 7,5, og
  - hvor, når koncentrationen af methylparaben er højere end 0,15 % (vægt/vægt),
  - 10 koncentrationen af carbomer er mindre end 1,25 % (vægt/vægt).
  
2. Topisk gelsammensætning ifølge krav 1, hvor den totale polyol omfatter ca. 4,5 % til 6,5 % (vægt/vægt) af en første polyol.
  
- 15 3. Topisk gelsammensætning ifølge krav 1, hvor carbomeren er udvalgt fra gruppen, der består af carbomer® 934P (syntetisk polymer af acrylsyre, der er tværbundet med polyalkenylethere eller divinylglycol), Carbopol® 974P (syntetisk polymer af acrylsyre, der er tværbundet med polyalkenylethere eller divinylglycol) og Carbopol® 980 (syntetisk polymer af acrylsyre, der er tværbundet med polyalkenylethere eller divinylglycol).
- 20
4. Topisk gelsammensætning ifølge krav 1, hvor sammensætningen omfatter:
  - 0,1 til 0,6 % (vægt/vægt) brimonidintartrat;
  - 0,05 til 0,15 % (vægt/vægt) methylparaben;
  - 0,80 til 1,50 % (vægt/vægt) carbomer;
  - 25 4,5 til 6,5 % (vægt/vægt) propylenglycol;
  - 4,5 til 6,5 % (vægt/vægt) glycerol og
  - oprenset vand;
  - hvor den topiske gelsammensætnings pH er justeret til 5,0 til 6,5 med en passende
  - mængde vandig natriumhydroxidopløsning.
  - 30
5. Topisk gelsammensætning ifølge krav 4, hvor sammensætningen omfatter mere end 0,3 (vægt/vægt) phenoxyethanol.

6. Topisk gelsammensætning ifølge krav 1 eller krav 5, der endvidere omfatter 0,04 til 0,08 % (vægt/vægt) af en vanddispergerbar form af titandioxid.
7. Topisk gelsammensætning ifølge et hvilket som helst af kravene 1-6 til anvendelse i  
5 behandling eller forebyggelse af en hudforstyrrelse hos et individ, hvor sammensætningen er beregnet til topisk påføring på et hudområde hos det individ, som er eller har tendens til at blive ramt af hudforstyrrelsen.
8. Topisk gelsammensætning til anvendelse ifølge krav 7, hvor hudforstyrrelsen er  
10 rosacea, rosacea med erytem, telangiectasi, psoriasis, purpura, akne med erytem, eksem, ikke-rosacea-relateret hudinflammation, rødmen, slap hud, hudfolder og/eller rynker eller et symptom, der er forbundet dermed.