Abstract: The present application relates to a stable topical composition comprising benzoyl peroxide in combination with one or more silicone compounds and a zinc compound. The present application further relates to the use of the topical composition as well as to a process for making such topical composition.
TOPICAL COMPOSITION FOR THE TREATMENT OF ACNE

FIELD OF THE INVENTION

[0001] The present application relates to a topical composition comprising benzoyl peroxide in combination with one or more silicone compounds and a zinc compound. The present application further relates to the use of the topical composition as well as a process for making such topical composition.

BACKGROUND OF THE INVENTION

[0002] Acne vulgaris (or simply acne) is a common human skin disease, characterized by areas of skin with seborrhea (scaly red skin), comedones (blackheads and whiteheads), papules (pinheads), nodules (large papules), pimples, and possibly causing scars. Acne affects integumentary system mostly skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back. Severe acne is inflammatory in nature, but acne can also manifest in non-inflammatory forms. The lesions are caused by changes in pilosebaceous units, skin structures consisting of a hair follicle and its associated sebaceous gland, changes that require androgen stimulation.

[0003] Acne scars are the result of inflammatory fibrous tissue that replaces normal skin after acne. Scar results from biological processes of wound repair in skin; wound tries to heal itself, resulting in too much accumulation of collagen in one spot.

[0004] Physical acne scars are often referred to as "ice pick" scars. This is because the scars tend to cause an indentation in the skin's surface. There is a range of treatments available. Although quite rare, the medical condition atrophia maculosa varioliformis cutis results in "acne-like" depressed scars on the face.

[0005] Ice pick scars: Deep pits that are the most common and a classic sign of acne scarring.

[0006] Box car scars: Angular scars that usually occur on the temple and cheeks, and can be either superficial or deep, these are similar to chickenpox scars.

[0007] Rolling scars: Scars that give to skin a wave-like appearance.

[0008] Hypertrophic scars: Thickened or keloid scars.

[0009] Many different treatments exist for acne including medications like benzoyl peroxide, antibiotics, retinoids, anti-seborrheic medications, anti-androgen medications, hormonal treatments, salicylic acid, alpha hydroxy acid, azelaic acid, nicotinamide, and keratolytic soaps. They are believed to work in at least 4 different ways, including: normalizing
shedding and sebum production into the pore to prevent blockage, killing *Propionibacterium acnes*, anti-inflammatory effects, and hormonal manipulation.

[0010] Benzoyl peroxide is a first-line treatment for mild and moderate acne due to its effectiveness and mild side-effects (mainly irritant dermatitis). It works against the "*P. acnes*" bacterium, helps prevent formation of comedones, and has anti-inflammatory properties. Benzoyl peroxide normally causes dryness of the skin, slight redness, and occasional peeling. Benzoyl peroxide has been found to be nearly as effective as antibiotics with all concentrations being equally effective. Unlike antibiotics, benzoyl peroxide does not appear to generate bacterial resistance. Benzoyl peroxide is often combined with antibiotics.

[0011] Silicone-based products represent one of the most common and effective solutions in preventing and treating hypertrophic acne scars. The silicone gel was introduced in the treatment of hypertrophic acne scars to overcome the difficulties in the management of silicone sheets. Indeed, the silicone gel has several advantages: it is transparent, quick drying, non-irritating and does not induce skin maceration; it can be used to treat extensive scars and uneven areas of skin. Silicone gels are popularly used for prevention of scar and keloid formation. However, prolonged exposure to silicone may cause dryness and skin irritation.

[0012] Several studies have been published on the individual effects of agents such as benzoyl peroxide, silicone and zinc compound on dermatological problems visible on the surface of the skin, such as non-inflamed comedones, inflamed papules and pustules, cutaneous infections, ingrown hairs, and keratotic scales (Handbook of Non-Prescription Drugs, American Pharmaceutical Association, 9th Ed. (1990) 798; Goodman and Gilman, Pharmacologic Basis of Therapeutics, MacMillan Publishing Co., 6th Ed. (1980), 977; Ruey, J. Y., Van Scott, E. J., U.S. Pat. No. 4,363,815). Various other literature available include those disclosing functionalized siloxanes for scar tissue treatment (WO 2005/105115), the treatment of acne scars with liquid silicone injections (Dermatol Surg. 2005 Nov; 31 (11 Pt 2): 1542-9), compositions comprising zinc compounds for acne and other skin inflammations (WO 2005/055927), and the clinical effects of zinc as a topical or oral agent on the clinical response and pathophysiologic mechanisms of acne (J Drugs Dermatol. 2013 May;12(5):542-5). Further, the patents U.S. Pat. Nos. 4,857,302, 5,445,823 and 5,648,389 disclose compositions comprising benzoyl peroxide wherein silicone copolymers, silicone oils and/or zinc compounds are employed as solubilizing agents, vehicle components and anti-irritating agents respectively.

[0013] Whilst silicones are useful for prevention and treatment of scars, these compounds on prolonged exposure may also cause skin problems such as dryness, irritation and itching.
As benzoyl peroxide also causes dryness of the skin, the concentration of silicones in benzoyl peroxide compositions may be critical. Further, a pH-balanced composition is desired wherein pH of the composition matches with the slightly acidic skin pH which is about 3 to about 6.

[0014] The available literature does not disclose a single topical composition comprising a combination of benzoyl peroxide, silicone compounds and zinc compounds, which is useful for the treatment of acne with simultaneous prevention and/or treatment of acne scars and other scars. It is also desired to have a composition that prevents skin problems such as dryness and irritation resulting from benzoyl peroxide application, and also has an enhanced stability.

[0015] Apart from these limitations, the process of preparing a topical composition comprising benzoyl peroxide in combination with a silicone compound is challenging. Benzoyl peroxide is temperature sensitive drug, and rheology of the silicone compounds is altered at higher temperatures (more than 30°C), while the process of preparation typically involves higher temperature during manufacturing process such as homogenization. The available literature does not appear to suggest any improved process that could overcome these process challenges.

[0016] There is a need for a single composition comprising a combination of benzoyl peroxide, siloxane and zinc compound, which can effectively treat acne and simultaneously prevent the formation of acne scars and other scars. Additionally it is desired to reduce dryness and skin inflammation or irritation, with an enhanced stability. There is a further need for a simple and improved process of manufacturing such a composition that can avoid the processing challenges, minimize the degradation of active drug with the acceptable quality attributes and aesthetic feel.

SUMMARY OF THE INVENTION

[0017] An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients.

[0018] Another aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients.

[0019] Another aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more
pharmaceutically acceptable excipients; wherein said composition comprises silicone to water in a weight ratio of from about 1:0.4 to about 1:1.5.

[0020] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; (d) a stabilizer selected from organic acids; and (e) one or more pharmaceutically acceptable excipients.

[0021] In one aspect of the present application, the topical composition is silicone-in-water emulsion.

[0022] In another aspect of the present application, the topical composition is an emulgel.

[0023] In another aspect of the present application, the topical composition comprises silicone-in-water emulsion and is in the form of an emulgel.

[0024] In one aspect of the present application, the hydrophobic phase is substantially free of non-silicone water-immiscible substances.

[0025] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof; the method comprising topically administering a composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; and (c) a zinc compound; wherein said inflammatory skin disorder and/or related condition is selected from acne, psoriasis, rosacea, dermatitis, erythema, actinic keratosism, and scars formed by the skin disorders.

[0026] In an aspect the said method prevents the formation of acne scars and other scars along with the treatment of acne, and/or treats existing acne scars and other scars along with the treatment of acne.

[0027] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof; the method comprising topically administering a composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; and (c) a zinc compound; wherein said composition is administered at least once daily to a subject in need thereof.

[0028] Another aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof; the method comprising topically administering a composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; and (c) a zinc compound; wherein said composition is administered two to three times daily to a subject in need thereof.

[0029] An aspect of the present application relates to a method of administering a topical composition comprising combination of benzoyl peroxide, one or more silicone compounds
and a zinc compound, to a subject in need thereof, the method comprises: (a) identifying a subject having an inflammatory skin disorder; and (b) topically administering said composition at least once daily for a period of from about one day to about 12 weeks, or until complete clearance of acne and/or acne scars and other scars, or as directed by physician; wherein said method provides therapeutically effective concentration of benzoyl peroxide in skin layers for at least about 5 hours from the application time.

[0030] Another aspect of the present application relates to a method of administering a topical composition comprising combination of benzoyl peroxide, one or more silicone compounds and a zinc compound, to a subject in need thereof, the method comprises: (a) identifying a subject having an inflammatory skin disorder; and (b) topically administering said composition two to three times daily for a period of from about one day to about 12 weeks, or until complete clearance of acne and/or acne scars and other scars, or as directed by physician; wherein said method provides therapeutically effective concentration of benzoyl peroxide in skin layers for at least about 5 hours from the application time.

[0031] An aspect of the present application relates to a process of preparing a topical composition comprising a combination of benzoyl peroxide, one or more silicone compounds, and a zinc compound, comprising steps of: (a) preparing a hydrophilic phase comprising benzoyl peroxide; (b) preparing a hydrophobic phase comprising one or more silicone compounds and a zinc compound; (c) emulsification of step (a) and step (b); wherein said process comprises temperature-controlled intermittent homogenization which prevents the degradation of benzoyl peroxide.

**BRIEF DESCRIPTION OF THE DRAWING**

[0032] **FIGURE 1:** Mean concentrations (in μg/gram of skin tissue) of benzoyl peroxide and benzoic acid after 8 hours of administration in rat skin samples. This figure shows that the compositions of present application (example 1 and example 2) provide benzoyl peroxide and benzoic acid concentrations similar to those of BENZAC AC®, and that the presence of silicones in the compositions of present application does not affect the concentration of benzoyl peroxide in the skin.

[0033] **FIGURE 2:** Comparative IVRT data of compositions of present application (example 3 and example 4) with BENZAC AC®. This figure shows that the in-vitro release of benzoyl peroxide from example 3 and example 4 composition is similar to that of BENZAC AC® in spite of presence of one or more silicone compounds.
FIGURE 3: Trans-epidermal water loss data of compositions of present applications (example 3 and example 4) in comparison with the blank skin. This figure shows that the compositions of present application minimize the moisture loss from the skin as compared to blank skin.

DETAILED DESCRIPTION

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skilled in the art.

The terms "effective amount" or "therapeutically effective amount" or "therapeutically effective concentration" as used herein refer to a non-toxic, but sufficient amount of the drug in the skin tissue, required for part or complete clearances of skin disorders in a subject.

The terms "about," or "generally," or "substantially," and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value. As used herein, the term "about," when referring to a value, or to an amount of mass, weight, time, volume, concentration or percentage, is meant to encompass variations of, in some aspects, +10%, in some aspects, +5%, in some aspects, +1%, in some aspects +0.5%, and in some aspects, +0.1% of the specified amount, as such variations are appropriate to perform the disclosed method.

The term "pH-balanced" as used herein refers to a composition having pH from about 3 to about 7. In some aspects, the pH of the topical composition of present application is from about 4 to about 6.

The terms "applying", "administering" or "administration", as used herein, refer to topical application of composition to affected and adjoining areas of skin by spreading or gentle rubbing or massaging.

The terms "topical composition" or "composition" as used herein refers to a topically administrable composition of present application. In some aspects, it refers to a topically administrable composition comprising a combination of benzoyl peroxide and one or more silicone compound. In some aspects, it refers to a topically administrable composition comprising a combination of benzoyl peroxide, one or more silicone compounds, and a zinc.
compound. In some aspects, the topical composition is in the form of semi-solid dosage form
or liquid dosage form, selected from, but not limited to, solution, emulsion, gel, cream, emulgel, ointment, lotion, spray or any suitable topical dosage form.

[0042] The term "emulgel" as used herein refers to a topical composition in the form of biphasic emulsion containing gelling agent, and in the form of thickened cream or gel, or in
other words it is called as a cream gel.

[0043] The terms "active", "active substance" "active agent" or "active ingredient" as used
herein refer to benzoyl peroxide or pharmaceutically acceptable forms of benzoyl peroxide. In
another aspect, the active substance refers to a combination of benzoyl peroxide, one or more
silicone compounds and a zinc compound in therapeutically effective concentrations.

[0044] The terms "related substance" or "impurity" as used herein refers to one or more
degradation substances of benzoyl peroxide during shelf life of the composition; or
intermediates or by-products occurring in the manufacturing process of benzoyl peroxide. In
some aspects, the impurity comprises one or more related substances selected from
benzaldehyde, benzoic acid, ethyl benzoate and one or more unknown impurities.

[0045] The term "skin disorder" as used herein refers to a disease condition of the skin. In
some aspects, the skin disorder refers to inflammatory skin disorders. In some aspects, the skin
disorder refers to acne or acne scars in a subject.

[0046] The term "stabilizer" as used herein refers to a chemical substance of organic or
inorganic nature that provides chemical, physical and/or polymorphic stability to the active
substance (i.e.) benzoyl peroxide and/or to the composition comprising the active substances.

[0047] The terms "acne" or "acne and related conditions" as used herein refer broadly to
inflammatory skin conditions such as acne vulgaris, acne conglobate, acne varioliformis, acne
tropica, infantile acne, acne excorice, unspecified acne or inflammation of acne or acne rosacea.

[0048] The term "acne scars" as used herein refers to the scars formed due to the formation
of acne on the skin and include post-acne scars, any existing or previously present scars, and
scars formed during the treatment period therein.

[0049] The term "other scars" as used herein include keloid scars, hypertrophic scars, scars
of rosacea, and scars formed by any other inflammatory skin conditions.

[0050] The term "subject" as used herein refers to any mammal such as human, rat, mouse,
monkey and the like. In an aspect, the subject is human. The term "subject" can be
interchangeably used with the term "patient". In an aspect, the term "subject" is used to denote
a human patient suffering from inflammatory skin disorder such as acne or scars of
inflammatory skin disorders.
[0051] The terms "excipient" or "topically acceptable excipient" or "pharmaceutically acceptable excipient" or "dermatologically acceptable excipient" are used interchangeably to mention any excipient which is acceptable for using in topical compositions and does not provide any therapeutic effect, and may contribute to aesthetic properties or any relevant nontherapeutic function of the topical composition.

[0052] In certain aspects, the terms compound, excipient, ingredient and agent, encompass both the singular and plural forms to indicate one or more such compounds, excipients, ingredients or agents.

[0053] The term "simultaneous prevention" as used herein means not allowing the scars to be formed during the period of treatment of acne. This term differs from the term "treatment" which refers to the treatment of already existing scars and the scars, if any, which are formed during or after the period of treatment of acne.

[0054] The term "substantial amount" as used herein indicates the amount of a compound present in the composition ranging from at least about 25%w/w to about 60%w/w based on the total weight of the composition. In an aspect, this term refers to the amount of the total silicone compounds of at least about 35%w/w based on the total weight of the composition.

[0055] The term "substantially free" as used herein indicates that the specified substance referred to is present in amounts not more than 10% by weight of the total composition or in amounts not more than about 9% by weight of the total composition, or in amounts not more than about 8% by weight of the total composition, or in amounts not more than about 7% by weight of the total composition, or in amounts not more than about 6% by weight of the total composition, or in amounts not more than about 5% by weight of the total composition, or in amounts not more than about 4% by weight of the total composition, or in amounts not more than about 3% by weight of the total composition, or in amounts not more than about 2% by weight of the total composition or in amounts not more than about 1% by weight of the total composition or in an amount about 0% by weight of the total composition or completely free of specified substance (i.e.) 0%.

[0056] The term "reference product" refers to an approved topical composition comprising benzoyl peroxide or its salts, solvates, enantiomers or mixtures thereof, at strengths of 5% and/or 2.5%. In an aspect, this term refers to a topical gel product marketed under the brand name BENZAC AC® at 5% and 2.5% strengths by Galderma, or any of its later approved pharmaceutical equivalents or its therapeutic equivalents or its bioequivalents.
The term "propellant-free" or "free of propellant(s)" as used herein indicates that the compositions are not delivered and/or not prepared using any of the commonly used aerosol propellants, such as fluorochloro hydrocarbons, hydrocarbons, compressed gases, and the like.

The present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients.

In one aspect of the present application, the topical composition comprises zinc compound in combination with a stabilizer, wherein the stabilizer provides chemical and/or physical stability to benzoyl peroxide.

In one aspect of the present application, the stabilizer is selected from organic acids, amino acids, fatty acids, inorganic acids and mixtures thereof.

In one aspect of the present application, the zinc compound in combination with the stabilizer provides enhanced stability to benzoyl peroxide.

In one aspect of the present application, the zinc compound in combination with the stabilizer provides enhanced stability to composition comprising benzoyl peroxide.

In another aspect of the present application, the stabilizer of the present application is selected from, but not limited to, straight or branched or saturated or unsaturated C2 to C20 acid, such as short chain carboxylic acid such as formic acid (HCOOH) to long chain fatty acid such as oleic acid. The stabilizer according to present application is selected from the group comprising, but not limited to, formic acid, lactic acid, acetic acid, dehydroacetic acid, maleic acid, fumaric acid, citric acid, anhydrous citric acid, citric acid monohydrate, ascorbic acid, isoascorbic acid, aspartic acid, benzenesulfonic acid, edetic acid, cyclamic acid, dihydroxybenzoic acid, glutamic acid, hydrochloric acid, oleic acid, linoleic acid, capric acid, lauric acid, palmitic acid, palmitoleic acid, stearic acid and mixtures thereof. In some aspects, the organic acid comprises suitable salt forms of acid and are selected from, but not limited to, sodium citrate, zinc lactate, and the like.

In another aspect of the present application, the stabilizer is selected from lactic acid and/or optimal isomers, salts thereof, citric acid and/or salts thereof.

In one aspect of the present application, the stabilizer is S-lactic acid.

In another aspect of the present application, the benzoyl peroxide is hydrous benzoyl peroxide. In all forgoing aspects, the percentage or concentration of benzoyl peroxide is expressed to denote anhydrous benzoyl peroxide. In some aspects, the benzoyl peroxide is present in the topical composition from about 0.5% w/w to about 15% w/w. In another aspect, the benzoyl peroxide is present from about 0.5% w/w to about 12% w/w. In another aspect, the
benzoyl peroxide is present in the concentration selected from, but not limited to, 2%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.1%, 5.2%, 5.3%, 5.4%, 5.5%, 5.6%, 5.7%, 5.8%, 5.9%, 6.0%, 6.1%, 6.2%, 6.3%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, 10%, 10.1%, 10.2%, 10.3%, 10.4%, 10.5%, 10.6%, 10.7%, 10.8%, 10.9%, 11%, 11.1%, 11.2%, 11.3%, 11.4%, 11.5%, 11.6%, 11.7%, 11.8%, 11.9%, or 12.0%.

[0067] In one aspect of the present application, the anhydrous benzoyl peroxide is present in the concentration of about 2.5% w/w and about 5% w/w based on the total weight of the composition; and the concentration of hydrous benzoyl peroxide is present in the concentration of about 3.36% w/w and about 6.66% w/w based on total weight of the composition.

[0068] In another aspect of the present application, the zinc compound is selected from zinc oxide, zinc sulfate, zinc lactate, silicone coated zinc salts, and the like.

[0069] In one aspect of the present application, the zinc compound is zinc oxide or zinc sulfate or mixtures thereof.

[0070] In another aspect of the present application, the silicone compound is one or more of the compounds including, but not limited to, polysiloxane compounds selected from cyclic siloxane such as cyclotetrasiloxane (octamethylcyclotetrasiloxane) also known as cyclomethicone, cyclopentasiloxane (decamethylcyclopentasiloxane), cyclohexasiloxane (dodecamethylcyclohexasiloxane), and mixtures thereof; or linear silicones such as dimethicone; or silicone elastomer such as polysilicone-11, cetearyl dimethicone/vinyl dimethicone crosspolymer, dimethicone/phenyl vinyl dimethicone crosspolymer, dimethicone/vinyl dimethicone crosspolymer or cyclopentasiloxane, and dimethicone crosspolymer; or silicone oils such as phenyl trimethicone and phenyl dimethicone; or any other forms of silicone compounds; and mixtures thereof.

[0071] In one aspect of the present application, the silicone compound is combination of two or more silicone compounds.

[0072] In one aspect of the present application, the silicone compound is elastomer 10.

[0073] In one aspect of the present application, the silicone compound is DC7040 (caprylyl methicone and polyethylene glycol-12 dimethicone/polypropylene glycol-20 crosspolymer).

[0074] In one aspect of the present application, the silicone compound is a linear chain silicone compound such as dimethicone.
In one aspect of the present application, the silicone compound is cyclomethicone.

In one aspect of the present application, the silicone compound is dimethiconol.

In some aspects, the silicone compound is present in an amount ranging from about 5% w/w to about 70% w/w based on the total weight of the composition. In some aspects, the silicone compound is present in an amount of at least about 10% w/w based on total weight of the composition.

In some aspects, the topical composition of the present application comprises substantial amount of total silicone compounds ranging from at least about 25% w/w to about 60% w/w based on the total weight of the composition.

In some aspects, the topical composition of the present application comprises substantial amount of total silicone compounds of at least about 35% w/w based on the total weight of the composition.

In some aspects, the topical composition of the present application is a monophasic composition.

In some aspects, the topical composition of the present application is in the form of a homogenous composition comprising one or more ingredients in suspended form.

In one aspect of the present application, the topical composition comprises benzoyl peroxide in suspended form.

An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients.

An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; (d) a stabilizer; and (e) one or more pharmaceutically acceptable excipients.

Topical composition of the present application comprises at least two immiscible phases. The hydrophilic phase comprises water, and one or more water-miscible substances, and the hydrophobic phase comprises one or more water-immiscible substances. The topical composition of the present application is in the form of an emulsion selected from oil-in-water or water-in-oil.

In another aspect, the hydrophilic phase comprises benzoyl peroxide and water.

In one aspect of the present application, the hydrophilic phase comprises benzoyl peroxide, a gelling agent, and water.
[0088] In another aspect, the hydrophobic phase comprises one or more silicone compounds.

[0089] In another aspect, the hydrophobic phase comprises one or more silicone compounds, and one or more water-immiscible substances.

[0090] In another aspect, the water-immiscible substance is selected from, but not limited to, vegetable oil, saturated paraffin oil, fatty acid, fatty alcohol, mineral oil, white wax, medium chain triglyceride and the like. Examples of the water-immiscible substance also include, but not limited to, oils of natural origin such as almond oil, coconut oil, olive oil, palm oil, peanut oil, fatty acids such as lauric acid, myristic acid, palmitic acid, and stearic acid, monohydric alcohol esters of the fatty acids such as ethyl laurate, isopropyl laurate, ethyl myristate, n-propyl myristate, isopropyl myristate, ethyl palmitate, isopropyl palmitate, methyl palmitate, methyl stearate, ethyl stearate, isopropyl stearate, butyl stearate, isobutyl stearate, amyl stearate, isoamyl stearate, branched or linear long chain aliphatic alcohols such as lauryl alcohol, myristyl alcohol, and stearyl alcohol, or mixtures thereof.

[0091] Examples of emollients include, but not limited to, caprylic/capric triglycerides, castor oil, ceteareth-20, ceteareth-30, cetearyl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, disopropyl adipate, glycerin, allantoin, glyceryl monooleate, glyceryl monostearate, glycercyl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white petrolatum, polyoxyethylene glycol fatty alcohol ethers, and mixtures thereof.

[0092] In one aspect of the present application, the hydrophobic phase comprises one or more silicone compounds and is substantially free of non-silicone water-immiscible substances.

[0093] In one aspect of the present application, the topical composition is a silicone-in-water emulsion.

[0094] In one aspect of the present application, the topical composition is an emulgel.

[0095] In another aspect of the present application, the topical composition comprises silicone-in-water emulsion and is in the form of an emulgel.

[0096] In another aspect, the topical composition comprises an emulsifying agent. The emulsifying agent is selected from, but not limited to, anionic surfactants, cationic surfactants, or non-ionic surfactants.

[0097] Anionic surfactants used in pharmaceutical preparations include, but not limited to, alkali-metal soaps (monovalent alkyl carboxylates) which are the sodium and potassium salts of the higher fatty acids. They are often produced from vegetable oils or from specific fatty
acids such as stearic acid, lauric acid, or oleic acid; animal fats such as tallow may also be used. Metallic soaps (polyvalent alkyl carboxylates), the calcium, zinc, magnesium, and aluminum salts of the higher fatty acids. Amine soaps, which are the amine salts of fatty acids and include trolamine (triethanolamine) stearate and diolamine (diethanolamine) stearate. Ester carboxylates, which are salts of fatty acids esterified with hydroxyacids or dicarboxylic acids; they include sodium stearoyl-lactylate and sodium stearyl fumarate. Alkyl sulfates (sulfated fatty alcohols; alkyl ester sulfates), such as sodium lauryl sulfate, which are the salts of sulfuric acid esters of fatty alcohols. Alkyl ether sulfates (ethoxylated alkyl sulfates) are similar compounds but the fatty alcohols are ethoxylated; examples include sodium laueth sulfate. Sulfated oils, which are vegetable and animal oils and fats that have been treated with sulfuric acid and then neutralized. Sulfated castor oil (neutralized with sodium hydroxide) has been widely used. Sulfonated compounds include alkyl sulfonates such as sodium caprylyl sulfonate and sodium cocoyl isetionate, and alkyl aryl sulfonates such as sodium dodecylbenzenesulfonate. Salts of sulfonated carboxylic acids such as sodium lauryl sulfoacetate disodium lauryl sulfosuccinate and docusate sodium (sodium dioctyl sulfosuccinate). Alkyl phosphates, including alkyl ester phosphates such as sodium lauryl phosphate and alkyl ether phosphates such as sodium lauryle phosphate. Alkyl sarcosidesor sarcosinatesare fatty acid amides produced from acylation of the synthetic amino acid sarcosine (N-methylglycine) with fatty acids. Salts such as sodium cocooyl sarcosinate and sodium lauroyl sarcosinate. Examples of anionic surfactants selected from, but not limited to, aluminium monostearate, calcium stearoyl-lactylate, sodium cetostearyl sulfate, sodium cocooyl isetionate, sodium cocooyl sarcosinate, sodium lauryl sulfate, sodium lauroyl isetionate, sodium lauroyl sarcosinate, sodium olate, sodium stearate, sodium stearoyl-lactylate, sulfated castor oil.

[0098] Cationic surfactants are used alone or in combination with other emulsifying agents. Examples of cationic surfactants include, but not limited to, tonzonium bromide.

[0099] Non-ionic surfactants are selected from, but not limited to, glycol and glycerol (glyceryl) esters: Simple esters of fatty alcohols and fatty acids have some surfactant properties but this can be improved by further hydroxyl or ester groups. Glycol and glycerol esters (monoesters of ethylene glycol, diethylene glycol, and propylene glycol, and mono- or diesters of glycerol) contain both ester and hydroxyl groups and are widely used as non-ionic surfactants. Macrogol esters: Polyethoxylation of glycols provides additional hydrophilicity, which increases with the degree of ethoxylation, and fatty acid esters with a wide range of macrogols (polyethylene glycols) are used. Glycol ethers: Ethers of glycols with fatty alcohols are generally included in the same class as macrogol ethers and are used similarly. Macrogol
ethers: Ethers of macrogols with fatty alcohols (macrogol alkyl ethers) or alkylphenols (macrogol aryl ethers) have similar properties to macrogol esters but the ether linkage is more stable to hydrolysis making macrogol ethers more resistant to acids and alkalis. Polyalcohol esters: Fatty acid esters of polyalcohols such as glycerol polymers (polyglycerols), sorbitol, and sucrose also have nonionic surfactant properties. Sorbitan esters (esters of the cyclic mono- or di-anhydrides of sorbitol with fatty acids) are oil-soluble, water-dispersible, nonionic surfactants and are effective water-in-oil emulsifiers. Polysorbates (polyethoxylated sorbitan esters) are more hydrophilic, water-soluble compounds and are used as oil-in-water emulsifying agents. Poloxamers are copolymers of polyoxyethylene and polyoxypropylene. Examples of non-ionic surfactants are selected from, but not limited to, acetoglycerides, diethylene glycol esters, diethylene glycol ethers, ethylene glycol esters, glycercyl behenate, glycercyl mono- and di-esters, glycercyl monocaprylocaprate, glycercyl monolinoleate, glycercyl mono-oleate, glycercyl stearates, macrogol cetostearyl ethers, macrogol/glycerol esters, macrogol 6 glyceryl caprylocaprate, macrogol 20 glyceryl monostearate, macrogol 15 hydroxystearate, macrogol laurates, macrogol lauryl ethers, macrogol monomethyl ethers, macrogol oleates, macrogol oleyl ethers, macrogol 40 sorbitol heptaoelate, macrogol stearates, macrogolglycerol cocoates, nonoxinols, octoxinols, oleyl oleate, palmitic acid, poloxamers, polyoxyxyl castor oils, polyoxyxyl hydrogenated castor oils, polysorbates, polyvinyl alcohol, propylene glycol caprylates, propylene glycol diacetate, propylene glycol laurates, propylene glycol monopalmitostearate, quillaia, sorbitan esters, sucrose esters, triglycerol disostearate, tyloxapol. Glycol and glycerol esters are selected from glycercyl behenate, glycercyl mono- and di-esters, glycercyl monocaprylocaprate, glycercyl monolinoleate, glycercyl mono-oleate, glycercyl distearate, glycercyl monostearate, glycercyl palmitostearate, diethylene glycol esters such as diethylene glycol monolaurate, diethylene glycol mono-oleate, diethylene glycol monostearate, diethylene glycol palmitostearate, ethylene glycol esters such as ethylene glycol distearate, ethylene glycol monopalmitostearate, propylene glycol esters such as propylene glycol dicaprylocaprate, propylene glycol monocaprylate, propylene glycol diacetate, propylene glycol dilaurate, propylene glycol monolaurate, propylene glycol monopalmitostearate, glycol ethers diethylene glycol ethers such as diethylene glycol monooethyl ether, macrogol derivatives such as ethoxylated glycerol esters, macrogol 6 glyceryl caprylocaprate, macrogol 20 glyceryl monostearate, macrogolglycerol cocoates, polyoxyxyl 35 castor oil, polyoxyxyl 40 hydrogenated castor oil, macrogol esters such as macrogol 15 hydroxystearate, macrogol laurates, macrogol oleates, macrogol stearates, macrogol/glycerol esters like behenoxy macrogolglycerides, caprylocaproyl macrogolglycerides, lauroyl
macrogolglycerides, linoleyl macrogolglycerides, oleoyl macrogolglycerides, stearoyl macrogolglycerides, macrogol alkyl ethers such as macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol aryl ethers such as nonoxinol 9, nonoxinol 10, nonoxinol 11, octoxinol 9, octoxinol 10, tyloxapol; polyalcohol esters such as polyglycerol esters, triglycerol diisostearate, sorbitan esters such as sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan sesquioleate, sorbitan stearate, sorbitan trioleate, sorbitan tristearate, sorbitan macrogol esters such as macrogol 40 sorbitol heptaoleate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 85, sucrose esters, poloxamers such as poloxalene, poloxamer 188, poloxamer 407.

[0100] In one aspect of the present application, the emulsifying agent is a non-ionic emulsifying agent.

[0101] In one aspect of the present application, the emulsifying agent is selected from poloxamer, polyoxyl 40 hydrogenated castor oil, and/or sodium lauryl sulfate.

[0102] In one aspect of the present application, the emulsifying agent is polyoxyl 40 hydrogenated castor oil.

[0103] In some aspects, the topical composition comprises one or more gelling agents. The gelling agents are selected from, but not limited to, carbomers, polyethylene glycols acrylate polymers, methacrylate polymers, polyvinylpyrrolidones, copolymers based on butyl methacrylate and methyl methacrylate povidone, vinyl acetates, polyvinyl acetates, celluloses, gums, alginates, cellulose acetate phthalates, cellulose acetate butyrates, hydroxypropyl methyl cellulose phthalates, and the like. Examples include commercially available products, such as, but not limited to, CARBOPOL® products, PEG 400, EUDRAGIT® 100, EUDRAGIT® RSPO, EUDRAGIT® RLPO, EUDRAGIT® ND40, PLASDONE®, Dry-FLO (aluminium starch octenyl succinate), Sepineo -P600 (a mixture of acrylamide acryloyldimethyl taurate copolymer, isohexadecane and polysorbate 80), copolymers based on butyl methacrylate and methyl methacrylate (PLASTOID® B), alkyl celluloses such as ethyl celluloses and methyl celluloses, hydroxyalkyl celluloses such as hydroxyethyl cellulose and hydroxypropyl cellulose, hydroxyalkyl alkyl celluloses such as hydroxypropyl methylcelluloses and hydroxy butyl methylcelluloses, gums such as xanthan gum, tragacanth, guar gum, locust bean gum, acacia, and the like and mixtures thereof.

[0104] In one aspect of the present application, the gelling agent is a mixture of acrylamide acryloyldimethyl taurate copolymer, isohexadecane and polysorbate 80, commercially known as SEPINEO-P600®.
In some aspects, the topical composition comprises one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients are selected from, but not limited to, moisturizers, humectants, solvents, co-solvents, emulsifying agents, solubilizing agents, amphiphilic substances, preservatives, buffers, skin penetration enhancers, gelling agents, antioxidants, film forming agents and the like.

In some aspects, the topical composition comprises a humectant selected from glycerine, sorbitol, xylitol, maltitol, polydextroses, urea, and the like.

In one aspect of the present application, the topical composition comprises glycerine as the humectant.

In an aspect, the topical composition of the present application is substantially free of (C1-C4) alcohols and/or propylene glycol, such that any amounts present do not cause significant skin irritation or impart any undesired attributes to the composition.

In another aspect, the composition of the present application is substantially free of glycols. The glycols according to the present application are alkylene or polyalkylene glycols. Examples include (C1 to C6) alkylene and polyalkylene glycols, such as ethylene glycol, polyethylene glycol (2 to 20 monomers), propylene glycol, dipropylene glycol, butylene glycol, pentylene glycol and hexylene glycol. They may or may not be oxyethylenated (2 to 50 EO). Also exemplary are glycol ethers, such as ethoxydiglycol or diethylene glycol monoethyl ether, marketed under the trademark Transcutol HP by Gattefosse, propylene glycol laurate marketed under the trademark Lauroglycol by Gattefosse, propylene glycol dicaprylate marketed under the trademark Estol 1526 by Uniqema, and propylene glycol dipelargonate.

In an aspect, the topical composition of the present application is propellant-free or substantially free of propellants.

An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; (d) a stabilizer; and (e) one or more pharmaceutically acceptable excipients; wherein said composition is a stable composition.

An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound (d) a stabilizer; and (e) one or more pharmaceutically acceptable excipients; wherein said composition is a stable composition.
[0113] In some aspects, the topical composition of the present application is stable for at least about 3 months. In some aspects, the topical composition is stable for at least about 6 months or for at least about 12 months. In some aspects, the topical composition is physically and chemically stable for a period of at least about 12 months when stored at 25°C/60%RH or at 30°C/65%RH.

[0114] In some aspects, the topical composition of the present application is pH-balanced composition having a pH ranging from about 3 to about 7.

[0115] In one aspect of the present application, the topical composition of the present application is pH-balanced composition having a pH from ranging about 4 to about 6.

[0116] In an aspect, the topical composition of the present application has a viscosity of about 4 poise to about 12 poise.

[0117] In an aspect, the topical composition of the present application is physically and chemically stable for at least about 12 months, wherein the composition comprises not more than about 10% of benzoic acid, and not more than about 1% of the total unknown impurities, and wherein the composition is pH-balanced and has a viscosity of about 4 poise to 12 poise, when tested for stability in about 12 months, under the conditions of 25°C/60%RH or at 30°C/65%RH. The viscosity was measured using Brookfield viscometer of CAP 2000+ model with spindle number 01 and spindle speed of and 50 rpm, at a temperature of 30°C, with run time of 100 seconds and hold time of 20Sec.

[0118] An aspect of the present application, a topical composition comprises: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; (d) a stabilizer; and (e) one or more pharmaceutically acceptable excipients; wherein said zinc compound and stabilizer is in the weight ratio of from about 1:1 to about 1:5.

[0119] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound (d) a stabilizer; and (e) one or more pharmaceutically acceptable excipients; wherein said zinc compound and stabilizer is in the weight ratio of from about 1:1 to about 1:5.

[0120] In some aspects, the weight ratio between the zinc compound and the stabilizer is selected from about 1:1 or 1:1.1 or 1:1.2 or 1:1.3 or 1:1.4 or 1:1.5 or 1:1.6 or 1:1.7 or 1:1.8 or 1:1.9 or 1:2 or 1:2.1 or 1:2.2 or 1:2.3 or 1:2.4 or 1:2.5 or 1:2.6 or 1:2.7 or 1:2.8 or 1:2.9 or 1:3.0 or 1:3.1 or 1:3.2 or 1:3.3 or 1:3.4 or 1:3.5 or 1:3.6 or 1:3.7 or 1:3.8 or 1:3.9 or 1:4.0. In an aspect, the zinc compound and the stabilizer are present in the weight ratio of about 1:2 or about 1:2.5 or about 1:3 or about 1:3.5 or about 1:4.
[0121] In one aspect of the present application, the zinc compound is zinc oxide, and the stabilizer is S-lactic acid having the weight ratio of about 1:1, or about 1:2.5, or about 1:3.

[0122] An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition provides therapeutically effective concentration of benzoyl peroxide for a period of at least about 5 hours in the skin layers of a subject.

[0123] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition provides therapeutically effective concentration of benzoyl peroxide for a period of at least about 5 hours in the skin layers of a subject.

[0124] In some aspects, the topical composition of the present application provides therapeutically effective concentration of benzoyl peroxide for a period of at least about 6 hours, or for a period of at least about 7 hours or for period of at least about 8 hours in the skin layers of a subject.

[0125] In one aspect of the present application, the therapeutically effective concentration of benzoyl peroxide provided by the topical composition of the present application is similar to that of BENZAC AC®.

[0126] In one aspect of the present application, the topical composition of the present application shows statistically similar concentration of benzoyl peroxide to that of BENZAC AC®.

[0127] In one aspect of the present application, the topical composition of the present application provides therapeutically effective concentration of benzoyl peroxide for a period of at least about 5 hours or up to about 12 hours in the skin layers of a subject.

[0128] An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition provides the mean cumulative percentage release of benzoyl peroxide of at least about 10% of applied dose in 6 hours.

[0129] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more
pharmaceutically acceptable excipients; wherein said composition provides the mean cumulative percentage release of benzoyl peroxide of at least about 10% of applied dose in 6 hours.

[0130] In some aspects, the topical composition provides the mean cumulative percentage release of benzoyl peroxide of at least about 0.5% of applied dose at half-an-hour, or at least about 2% of applied dose at 1 hour, or at least about 5% of applied dose at 2 hours, or at least about 7% of applied dose at 3 hours, or at least about 9% of applied dose at 4 hours, or at least about 10% of applied dose at 6 hours.

[0131] In one aspect of the present application, the mean cumulative percentage release of benzoyl peroxide from the topical composition of the present application is similar to that of BENZAC AC®.

[0132] In one aspect of the present application, the topical composition comprises: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the mean cumulative percentage release of benzoyl peroxide from the topical composition of the present application is similar to that of BENZAC AC®; and said silicone compound is present in an amount of at least about 10% w/w based on the total weight of the composition.

[0133] In one aspect of the present application, a topical composition comprises: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the mean cumulative percentage release of benzoyl peroxide from the topical composition of the present application is similar to that of BENZAC AC®; and said silicone compound is present in an amount of at least about 10% w/w based on the total weight of the composition.

[0134] In one aspect of the present application, the topical composition provides similar mean cumulative percentage release of benzoyl peroxide as compared to non-silicone topical composition of benzoyl peroxide (i.e.) BENZAC AC®.

[0135] In one aspect of the present application, the topical composition comprises: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition provides the mean cumulative percentage release of benzoyl peroxide at least about 10% of applied dose at 6 hours, when subjected to in-vitro release study using a synthetic cellulose nitrate membrane with 0.22 micron thickness, and the receptor fluid is Phosphate-buffered saline (PBS buffer)
and ethanol (50:50) v/v of polyethylene glycol 400, and applied composition weight is about 50 mg.

[0136] In one aspect of the present application, a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition provides the mean cumulative percentage release of benzoyl peroxide at least 10% of applied dose at 6 hours, when subjected to in-vitro release study using a synthetic cellulose nitrate membrane with 0.22 micron thickness, and the receptor fluid is Phosphate-buffered saline (PBS buffer) and ethanol (50:50) v/v of polyethylene glycol 400, and applied composition weight is about 50 mg.

[0137] An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition is occlusive to the skin.

[0138] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition is occlusive to the skin.

[0139] In another aspect, the topical composition is occlusive, wherein said composition provides average moisture loss of not more than about 5 g/m²h after about 6 hours from the application time in trans-epidermal water loss study.

[0140] In another aspect, the topical composition is occlusive, wherein said composition reduces trans-epidermal water loss by at least about 20% after about 6 hours as compared to that of the unapplied skin, otherwise called as blank skin.

[0141] An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compound; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio of benzoyl peroxide to silicone compound is from about 1:4 to about 1:10.

[0142] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio of benzoyl peroxide to silicone compound is from about 1:4 to about 1:10.
In one aspect of the present application, the weight ratio between benzoyl peroxide to silicone compound is about 1:4, or about 1:5, or about 1:6, or about 1:7, or about 1:8, or about 1:9, or about 1:10.

An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio of zinc compound to benzoyl peroxide is from about 1:2 to about 1:17.

An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio of zinc compound to benzoyl peroxide is from about 1:2 to about 1:17.

In one aspect of the present application, the weight ratio between zinc compound to benzoyl peroxide is about 1:3, or about 1:4, or about 1:5, or about 1:6, or about 1:7.

An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio between benzoyl peroxide to silicone compounds to zinc compound is selected from 3:30:1, 3:35:1, 3:40:1, 3:45:1, 4:30:1, 4:35:1, 4:40:1, 4:45:1, 5:30:1, 5:35:1, 5:40:1, 5:45:1, 6:30:1, 6:35:1, 6:40:1, 6:45:1, 7:30:1, 7:35:1, 7:40:1, and 7:45:1.

An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein the weight ratio between benzoyl peroxide to silicone compounds to zinc compound is selected from 3:30:1, 3:35:1, 3:40:1, 3:45:1, 4:30:1, 4:35:1, 4:40:1, 4:45:1, 5:30:1, 5:35:1, 5:40:1, 5:45:1, 6:30:1, 6:35:1, 6:40:1, 6:45:1, 7:30:1, 7:35:1, 7:40:1, and 7:45:1.

In one aspect of the present application, the weight ratio between benzoyl peroxide to silicon compounds to zinc compound is selected from about 3:35:1, about 4:35:1, about 5:45:1, about 6:45:1, about 7:45:1, about 5:35:1, about 6:35:1, and about 7:35:1.

An aspect of the present application relates to a topical composition comprising: (a) benzoyl peroxide; (b) one or more silicone compound; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition comprises at least about 10% w/w of a silicone compound based on total weight of the composition.
[0151] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition comprises at least about 10% w/w of a silicone compound based on total weight of the composition.

[0152] In some aspects, the topical composition comprises one or more silicone compounds in an amount of at least about 15% w/w, or at least about 20% w/w, or at least about 25% w/w, or at least about 30% w/w, or at least about 35% w/w, or at least about 40% w/w, or at least about 45% w/w, or at least about 50% w/w or at least about 55% w/w, or at least about 60% w/w based on total weight of the composition.

[0153] In one aspect of the present application, the topical composition comprises substantial amounts of one or more silicone compounds, wherein said composition is occlusive and provides the retention of moisture content and prevents irritation/dryness to the subject’s skin.

[0154] In one aspect of the present application, the topical composition is easily water-washable and non-greasy.

[0155] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition comprises water in an amount of at least about 10% w/w.

[0156] An aspect of the present application relates to a topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition comprises water in an amount of at least about 10% w/w.

[0157] In some aspects, the topical composition comprises water in an amount of at least about 15% w/w, or at least about 20% w/w, or at least about 25% w/w, or at least about 30% w/w, or at least about 35% w/w, or at least about 40% w/w, or at least about 45% w/w, or at least about 50% w/w based on total weight of the composition.

[0158] In some aspects, the composition comprises one or more silicone compounds in an amount of at least about 10% w/w, or at least about 15% w/w, or at least about 20% w/w, or at least about 25% w/w, or at least about 30% w/w, or at least about 35% w/w, or at least about
40% w/w, or at least about 45% w/w, or at least about 50% w/w or at least about 55% w/w, or
at least about 60% w/w based on total weight of the composition.

[0159] In one aspect of the present application, the topical composition has a weight ratio
of silicone to water from about 1:0.4 to about 1:1.5.

[0160] An aspect of the present application relates to a topical composition comprising: (a)
a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase
comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more
pharmaceutically acceptable excipients; wherein said composition is silicone-in-water
emulsion and has a silicone-to-water weight ratio from about 1:0.4 to about 1:1.5.

[0161] An aspect of the present application relates to a topical composition comprising:
(a) benzoyl peroxide; (b) one or more silicone compounds; (c) a zinc compound; and (d) one
or more pharmaceutically acceptable excipients; wherein said composition has a silicone-to-
water weight ratio from about 1:0.4 to about 1:1.5.

[0162] An aspect of the present application relates to a topical composition comprising: (a)
benzoyl peroxide in an amount of from about 1% w/w to about 12% w/w; (b) one or more
silicone compounds in an amount of from about 10% w/w to about 60% w/w; (c) a zinc
compound in an amount of from about 0.5% w/w to about 5% w/w; (d) a stabilizer; and one or
more pharmaceutically acceptable excipients; wherein the stabilizer is lactic acid.

[0163] An aspect of the present application relates to a topical composition comprising: (a)
a hydrophilic phase comprising benzoyl peroxide in an amount of from about 1% w/w to about
12% w/w and water; (b) a hydrophobic phase comprising one or more silicone compounds in
an amount of from about 10% w/w to about 60% w/w; (c) a zinc compound in an amount of from
about 0.5% w/w to about 5% w/w; (d) a stabilizer; and one or more pharmaceutically acceptable
excipients; wherein the stabilizer is lactic acid.

[0164] In one aspect of the present application, one or more silicone compounds are
selected from elastomer-10, dimethicone, cyclomethicone, dimethicone crosspolymers and
mixtures thereof.

[0165] In one aspect of the present application, the zinc compound is selected from zinc
oxide, zinc sulfate, zinc lactate and mixtures thereof.

[0166] An aspect of the present application relates to a process of preparing a topical
composition comprising a combination of benzoyl peroxide, and one or more silicone
compound, comprising: (a) preparing an active substance phase comprising benzoyl peroxide
with one or more gelling agents; (b) preparing a dispersion containing one or more silicone
compounds; (c) blending of step (a) and step (b) to prepare homogenous monophasic dispersion; and (d) filling the composition of step (c) into a suitable dispensing device.

[0167] An aspect of the present application relates to a process of preparing a topical composition comprising a combination of benzoyl peroxide, and one or more silicone compound, comprising: (a) preparing a hydrophilic phase comprising benzoyl peroxide; (b) preparing a hydrophobic phase comprising one or more silicone compound; (c) adding the dispersion of step (b) to step (a); and (d) filling the composition of step (c) into a suitable dispensing device.

[0168] The process of preparing topical composition comprising benzoyl peroxide in combination with silicone compound is challenging, because benzoyl peroxide is temperature sensitive active substance and degrades in higher temperatures during the process of preparing hydrophilic phase and emulsification. The rheology of the silicone compounds is altered at higher temperatures (more than about 30°C) and the process of preparing pharmaceutical dosage forms such as emulsion, typically involves higher temperature during manufacturing process (exothermic process) while homogenization. The process of preparation according to the present application involves temperature controlled process and intermittent homogenization. The intermittent homogenization process is the process of homogenization followed in the steps of hydrophilic phase preparation and emulsification, wherein the homogenization is carried out below 20°C throughout the process, and the homogenization is stopped in between whenever the temperature of the process goes above 20°C. The temperature of the process is controlled using a device such as chilled water circulating-jacketed manufacturing vessel, or any suitable other methods of controlling temperature. The intermittent homogenization process is essential for preparing composition comprising temperature sensitive drugs such as benzoyl peroxide, and this intermittent homogenization process along with temperature controlled device are important to carry out the process of preparing topical composition comprising benzoyl peroxide and silicone compounds. The temperature is continuously monitored during the process.

[0169] The process of preparing a topical composition of the present application is temperature-controlled and involves intermittent homogenization, wherein the temperature is maintained below about 20°C in order to prevent the degradation of benzoyl peroxide.

[0170] In one aspect of the present application, the intermittent homogenization is a temperature-controlled process carried out below about 20°C to about 10°C with the homogenization speed of about 2500 rpm to about 10000 rpm.
In some aspects, the intermittent homogenization involves homogenization at 2500 rpm to 10000 rpm with a temperature below about 20°C.

[0172] In some aspects, the step of preparing hydrophilic phase is carried out at a low temperature below about 20°C to about 10°C.

[0173] An aspect of the present application relates to a process of preparing a topical composition comprising a combination of benzoyl peroxide, one or more silicone compound, and a zinc compound, wherein said process comprises steps of: (a) preparing a hydrophilic phase comprising benzoyl peroxide, an emulsifying agent, and water with intermittent homogenization at temperatures below about 20°C; (b) preparing a hydrophobic phase comprising one or more silicone compound and a zinc compound; (c) emulsification of dispersion from step (a) and step (b) with intermittent homogenization at a temperature below about 20°C; and (d) dispensing the composition of step (c) in a suitable device; wherein the intermittent homogenization is carried out to keep the temperature below about 20°C.

[0174] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder, comprising a step of administration of a topical composition comprising: benzoyl peroxide, one or more silicone compound, and a zinc compound.

[0175] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof, comprising a step of administration of a topical composition comprising: benzoyl peroxide, one or more silicone compounds, and a zinc compound.

[0176] In some aspects, the inflammatory skin disorder is selected from, but not limited to, acne, psoriasis, rosacea, dermatitis, erythema, actinic keratosis, and the like.

[0177] In some aspects, the inflammatory skin disorder and/or related conditions thereof is selected from acne, psoriasis, rosacea, dermatitis, erythema, actinic keratosis, and scars formed by the skin disorders.

[0178] In one aspect of the present application, the inflammatory skin disorder is acne vulgaris.

[0179] In one aspect of the present application, the inflammatory skin disorder and/or related conditions thereof include acne vulgaris and acne scars.

[0180] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder, comprising topical administration of a composition comprising benzoyl peroxide, one or more silicone compounds, and a zinc compound, wherein said method provides therapeutically effective concentration of benzoyl peroxide similar to that of BENZAC AC® in the skin layers of a subject.
[0181] An aspect of the present application relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof, comprising topical administration of the composition comprising benzoyl peroxide, one or more silicone compounds, and a zinc compound, wherein said method provides therapeutically effective concentration of benzoyl peroxide similar to that of BENZAC AC® in the skin layers of a subject.

[0182] In one aspect of the present application, the method relates to simultaneous treatment and/or prevention of inflammatory skin disorder and related conditions thereof.

[0183] In one aspect of the present application, the method relates to simultaneous treatment and/or prevention of acne and acne scars and other scars in a subject.

[0184] In an aspect, the present application relates to a method of treatment and/or prevention of acne and other skin inflammation associated with acne with simultaneous prevention and/or treatment of acne scars and other scars, comprising topically administering a composition comprising benzoyl peroxide, one or more silicone compounds, and a zinc compound from about one day to about 12 weeks, or up to the clearance of the skin disorder, wherein said method provides therapeutically effective concentration of benzoyl peroxide for at least about 5 hours in the skin layers of a subject.

[0185] In some aspects, the method comprises administration of the topical composition from about one day to about 12 weeks, or up to the clearance of the skin disorder.

[0186] In one aspect of the present application, the method prevents the formation of acne scars and other scars along with the treatment of acne, and treats the existing acne scars along with the treatment of acne.

[0187] An aspect of the present application relates to a method of administering a topical composition comprising combination of benzoyl peroxide, one or more silicone compound and a zinc compound, to a subject in need thereof, the method comprising: (a) identifying a subject having an inflammatory skin disorder; and (b) topically administering said composition at least once daily for a period of from about one day to about 12 weeks, or until complete clearance of acne and/or acne scars and other scars, or as directed by physician.

[0188] An aspect of the present application relates to a method of administering a topical composition comprising combination of benzoyl peroxide, one or more silicone compound and a zinc compound, to a subject in need thereof, the method comprising: (a) identifying a subject having an inflammatory skin disorder; and (b) topically administering said composition two to three times daily for a period of from about one day to about 12 weeks, or until complete clearance of acne and/or acne scars and other scars, or as directed by physician.
In one aspect of the present application, the method comprises administration of the topical composition once daily to the subject.

In one aspect of the present application, the method comprises administration of the topical composition twice daily to the subject.

In one aspect of the present application, the method provides a therapeutically effective concentration of benzoyl peroxide similar to that of BENZAC AC®.

In one aspect of the present application, the method provides a therapeutically effective concentration of benzoyl peroxide at least for a period of about 5 hours or up to about 12 hours in the skin layers of a subject.

In an aspect, the topical composition is physically and chemically stable for at least about 12 months, wherein the composition comprises not more than about 10% of the benzoic acid, and not more than about 1% of the total unknown impurities, when tested for stability in 12 months, under the conditions of 25°C/60%RH or at 30°C/65%RH.

The following examples further describe certain specific aspects of the application.

**EXAMPLES**

The following examples are provided to illustrate certain specific aspects of the present application, and should not be construed to limit the scope of the application in any manner. The following examples may include compilations of data that are representative of data gathered at various time points during the course of development and experimentation related to the present application.

Topical compositions comprising benzoyl peroxide, one or more silicone compounds and a zinc compound were manufactured, and are illustrated as Examples 1-5 in Table 1.

Table 1: Topical compositions comprising benzoyl peroxide, silicone compound and zinc compound

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Ingredients</th>
<th>Example-1 % w/w</th>
<th>Example-2 % w/w</th>
<th>Example-3 % w/w</th>
<th>Example-4 % w/w</th>
<th>Example-5 % w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrous benzoyl peroxide</td>
<td>6.66</td>
<td>6.66</td>
<td>6.66</td>
<td>3.36</td>
<td>6.66</td>
</tr>
<tr>
<td>2</td>
<td>Elastomer 10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>DC7040</td>
<td>10</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Cyclomethicone</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Dimethicone 350 cSt</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>Zinc oxide</td>
<td>1.044</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Zinc sulfate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>No.</td>
<td>Ingredient</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>8</td>
<td>Poloxamer 188</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sodium lauryl sulfate</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Polysorbate-80</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Polyoxyl 40 Hydrogenated Castor Oil</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Glycerin</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>S-Lactic acid</td>
<td>2.5</td>
<td>2.5</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Sepineo-P600</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>Purified water</td>
<td>30.596</td>
<td>33.84</td>
<td>43.34</td>
<td>46.64</td>
<td>35.34</td>
</tr>
</tbody>
</table>

The percentages of hydrous benzoyl peroxide 6.66% is equivalent to 5% of anhydrous benzoyl peroxide, and 3.36% is equivalent to 2.5% of anhydrous benzoyl peroxide; Elastomer 10 is a mixture of high molecular weight silicon elastomer (contained up to 12%) and remaining portion is decamethylcyclopentasiloxane; Sepineo-P600 is a mixture of acrylamide acryloyldimethyl taurate copolymer, isohexadecane and polysorbate 80; DC7040 is caprylyl methicone and polyethylene glycol-12 dimethicone/polypropylene glycol-20 crosspolymer.

[0198] Preparing hydrophilic phase: A stainless steel vessel was charged with purified water and homogenization was carried out at 2500-3000 rpm, further poloxamer 188 was dissolved under homogenization for 15 minutes under controlled temperature 10°C - 20°C in the stainless steel vessel to form a dispersion and glycerine was added to the dispersion followed by hydrous benzoyl peroxide under continuous homogenization maintaining temperature 10°C - 20°C, and finally polyoxyl 40 hydrogenated castor oil was added to the benzoyl peroxide dispersion of step 3 under homogenization maintaining temperature 10°C - 20°C. Homogenization was continued for 30 minutes.

[0199] Preparing hydrophobic phase: The hydrophobic phase was prepared separately in main manufacturing vessel. The vessel was charged with silicone compounds (elastomer- 10, DC7040, cyclomethicone, and/or dimethicone 350 cSt), S-lactic acid and mixed to form homogenous dispersion and the zinc compound was dispersed in above the dispersion containing silicones and mixed to form a uniform dispersion of hydrophobic silicone phase.

[0200] Emulsification: The hydrophobic phase was transferred to hydrophilic phase under homogenization maintaining temperature 10°C - 20°C and continued homogenization for 1 hour. Finally Sepineo-P 600 was added to the above dispersion and further homogenized for 1 hour and the emulsion was homogenized at 500 rpm for 30 minutes.

[0201] The composition obtained from the above process was filled suitable container closure system such as Lami Tube. The process of the above examples were prepared by intermittent homogenization and temperature-controlled process below 20°C.
[0202] Example 6: Comparative Pharmacokinetics of composition of the Example 1 and Example 2 and the reference product (BENZAC AC® 5%) in Male Sprague Dawley Rats

[0203] Pharmacokinetic study protocol: The protocol was to estimate the concentrations of benzoyl peroxide (BPO) and benzoic acid in rat skin after single topical application of compositions of example 1 and example 2 at specified time period (8 hours), in comparison to the reference product BENZAC AC® 5%, in male Sprague Dawley rats.

[0204] Male Sprague Dawley rats (180 - 230 g) were used in the study. Total three groups were formed containing 18 rats in each group of example 1, example 2 and BENZAC AC® and each rat were administered 50mg of compositions topically. Dorsal region of each rat was shaved (2.5 x 2.5 cm2) and area of 2 x 2 cm2 was marked with help of marker. Skin was wiped with acetone to remove sebum. A 50 mg of compositions was weighed in aluminium foil and applied on the marked area, spread uniformly and left for 30 min and later covered with the help of adhesive tape. Skin samples were collected at 8 hours' time point post application and homogenised at respective intervals. The collected homogenate skin samples were analysed for benzoyl peroxide and benzoic acid using an analytical method involving HPLC-UV.

[0205] Table 2: Summary of mean concentrations of benzoyl peroxide and benzoic acid (μg/g) in rat skin samples

<table>
<thead>
<tr>
<th>Compositions</th>
<th>Time point (hr)</th>
<th>Benzoyl Peroxide concentration (μg/g)</th>
<th>Benzoic Acid concentration (μg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Product (5%) (BENZAC AC®)</td>
<td>8</td>
<td>146 ± 191</td>
<td>367 ± 207</td>
</tr>
<tr>
<td>Example-1 (benzoyl peroxide 5%)</td>
<td>8</td>
<td>147 ± 101</td>
<td>339 ± 78.8</td>
</tr>
<tr>
<td>Example-2 (benzoyl peroxide 5%)</td>
<td>8</td>
<td>120 ± 90.7</td>
<td>326 ± 86.4</td>
</tr>
</tbody>
</table>

* - note the strength of benzoyl peroxide is expressed as anhydrous benzoyl peroxide concentration in compositions (example 1, example 2 and reference product)

[0206] Example 1 and 2 compositions of the present application showed comparable benzoyl peroxide and benzoic acid exposures to the reference product in at 8hrs after dosing. It was observed that the release of benzoyl peroxide was not affected by the presence of silicones in the compositions of example 1 and 2, as against the reference product which does not contain any silicone compound.

[0207] Example 7: The in-vitro release studies (IVRT) of compositions of example 3 and example 4
This in-vitro active substance release from composition was studied in comparison with BENZAC AC®. The release rate of benzoyl peroxide from reference product (BENZAC AC®) was compared with release rates of compositions (Examples 3 and 4) of the present application, across a synthetic membrane.

IVRT study parameters: The receptor fluid was phosphate buffer with ethanol (50:50) in polyethylene glycol 400 medium, the membrane was cellulose nitrate (0.22µ), temperature: 32° C ± 1°C. The samples were tested using HPLC method.

The steady state release was observed for the examples 3 and 4, and was found to be comparable with the reference product.

Table 3: Comparative IVRT data of example 3 and example 4, and BENZAC AC®

<table>
<thead>
<tr>
<th>Product</th>
<th>Example 3 (5% benzoyl peroxide)</th>
<th>BENZAC AC® 5%</th>
<th>Example 4 (2.5% benzoyl peroxide)</th>
<th>BENZAC AC® 2.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point (Hr)</td>
<td>Mean (n:3)</td>
<td>Mean (n:3)</td>
<td>Mean (n:3)</td>
<td>Mean (n:3)</td>
</tr>
<tr>
<td>1</td>
<td>1.1</td>
<td>1.37</td>
<td>3.3</td>
<td>3.9</td>
</tr>
<tr>
<td>2</td>
<td>3.47</td>
<td>4.37</td>
<td>9.27</td>
<td>10.33</td>
</tr>
<tr>
<td>3</td>
<td>6.13</td>
<td>7.7</td>
<td>15</td>
<td>15.7</td>
</tr>
<tr>
<td>4</td>
<td>8.6</td>
<td>10.8</td>
<td>20.33</td>
<td>20.47</td>
</tr>
<tr>
<td>5</td>
<td>11.07</td>
<td>13.93</td>
<td>25.1</td>
<td>24.77</td>
</tr>
<tr>
<td>6</td>
<td>13.53</td>
<td>17.07</td>
<td>29.63</td>
<td>28.83</td>
</tr>
</tbody>
</table>

Example 8: Stability studies

The prepared compositions of examples 3 and 4 (comprising lactic acid) and example 5 (devoid of lactic acid) were filled into closed container and exposed to the stability testing conditions 25°C and 60% RH and 30°C and 65% RH, and analyses at various storage points are shown in Table 4-6.

Table 4: Stability testing of Example 3

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Initial</th>
<th>3 M 30°C/65% RH</th>
<th>3 M 25°C/60% RH</th>
<th>6 M 30°C/65% RH</th>
<th>6 M 25°C/60% RH</th>
<th>12 M 30°C/65% RH</th>
<th>12 M 25°C/60% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Assay</td>
<td>98.4</td>
<td>98.2</td>
<td>98.7</td>
<td>98.4</td>
<td>100.1</td>
<td>97.5</td>
<td>99.9</td>
</tr>
<tr>
<td>Benzoic acid*</td>
<td>0.4</td>
<td>1.24</td>
<td>0.89</td>
<td>1.88</td>
<td>1.06</td>
<td>4.47</td>
<td>2.4</td>
</tr>
<tr>
<td>Total unknown impurities</td>
<td>0.06</td>
<td>0.06</td>
<td>0.08</td>
<td>0.04</td>
<td>0.04</td>
<td>0.09</td>
<td>0.04</td>
</tr>
</tbody>
</table>
### Table 5: Stability testing of Example 4

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Initial</th>
<th>3 M 30°C/65% RH</th>
<th>3 M 25°C/60% RH</th>
<th>6 M 30°C/65% RH</th>
<th>6 M 25°C/60% RH</th>
<th>12 M 30°C/65% RH</th>
<th>12 M 25°C/60% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Assay</td>
<td>99.4</td>
<td>98.2</td>
<td>99</td>
<td>97.1</td>
<td>100.1</td>
<td>93.3</td>
<td>98</td>
</tr>
<tr>
<td>Benzoic acid*</td>
<td>0.5</td>
<td>2.13</td>
<td>1.32</td>
<td>3.35</td>
<td>1.87</td>
<td>8.23</td>
<td>4.07</td>
</tr>
<tr>
<td>Total unknown impurities</td>
<td>0.06</td>
<td>0.07</td>
<td>0.07</td>
<td>0.06</td>
<td>0.06</td>
<td>0.16</td>
<td>0.1</td>
</tr>
<tr>
<td>Viscosity (Poise)</td>
<td>6.15</td>
<td>4.58</td>
<td>7.76</td>
<td>7.54</td>
<td>7.87</td>
<td>8.02</td>
<td>7.5</td>
</tr>
<tr>
<td>pH</td>
<td>4.66</td>
<td>4.61</td>
<td>4.53</td>
<td>4.18</td>
<td>4.16</td>
<td>4.19</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* - benzoic acid is a related substance, and often called as impurity B of benzoyl peroxide

### Table 6: Stability testing of Example 5

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Initial</th>
<th>1 M 30°C/65% RH</th>
<th>1 M 25°C/60% RH</th>
<th>2 M 30°C/65% RH</th>
<th>2 M 25°C/60% RH</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Assay</td>
<td>95.1</td>
<td>94.7</td>
<td>93.5</td>
<td>95.7</td>
<td>96.5</td>
</tr>
<tr>
<td>Benzoic acid*</td>
<td>0.63</td>
<td>1.31</td>
<td>1.7</td>
<td>2.13</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Total unknown impurities</td>
<td>1.26</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Viscosity (Poise)</td>
<td>18.36</td>
<td>19.61</td>
<td>18.82</td>
<td>17.29</td>
<td>17.25</td>
</tr>
<tr>
<td>pH</td>
<td>6.65</td>
<td>6.39</td>
<td>5.16</td>
<td>4.41</td>
<td>4.72</td>
</tr>
</tbody>
</table>

* - benzoic acid is a related substance, and often called as impurity B of benzoyl peroxide; ND- not detected

**[0215]** The Examples 3 and 4 were found to be stable with respect to benzoic acid and other unknown impurities which were maintained well within the limits, and the both compositions were lactic acid (stabilizer)- containing compositions. It was observed that the Example 5 (devoid of stabilizer) composition was relatively unstable with the increased benzoic acid and total unknown impurities, imbalanced pH, and increased viscosity found within the time period of 2 months. The presence or increase in lactic acid concentration has improved the stability with reduced impurities, balance in the pH and viscosity.

**[0218]** Example 9: Trans-epidermal water loss (TEWL) study
Trans-epidermal water loss (TEWL) study was conducted with the aim to investigate the influence of compositions of Example 3 (5% benzoyl peroxide) and Example 4 (2.5% benzoyl peroxide) on the TEWL of the skin. All the compositions were applied to the surface of dermatomed human skin. This experimental study helped in understanding the TEWL of skin after application of compositions of the present application on human skin.

Methods and materials: The dermatomed human skin samples were obtained from 45 years old, male, and the skin was thawed to room temperature and was cut down into pieces sufficient enough to cover the receptor chamber completely. The receptor chamber was filled with phosphate buffer. The compositions were applied on the epidermal side of the skin.

About 25 mg of the formulation was applied on the surface of the skin and gently rubbed to spread it uniformly. Practically it was observed that, the applied amount was sufficient to completely spread the formulation uniformly over the skin. This procedure is to mimic the actual application condition. TEWL readings were recorded before application of the sample and after 6 hours from the time of application.

Table 7: TEWL data

<table>
<thead>
<tr>
<th>Study products</th>
<th>Average TEWL (g/m²h)</th>
<th>Percentage change in TEWL after 6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial (prior application)</td>
<td>6 hours (after application)</td>
</tr>
<tr>
<td>Blank skin</td>
<td>7.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Example 3</td>
<td>4.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Example 4</td>
<td>4.4</td>
<td>3.3</td>
</tr>
</tbody>
</table>

The TEWL of the compositions of example 3 and example 4 were found to be reduced by 26.32% and 33.33% respectively after 6 hours of topical application, as compared to that of the blank skin as a control which was found to be increased by 3.7%. This suggests that compositions of example 3 and example 4 of the present application minimize the TEWL and thus retain the skin moisture and prevent the skin dryness. It was concluded that the compositions of the present application were occlusive in nature.
We claim:

1. A topical composition comprising: (a) a hydrophilic phase comprising benzoyl peroxide and water; (b) a hydrophobic phase comprising one or more silicone compounds; (c) a zinc compound; and (d) one or more pharmaceutically acceptable excipients; wherein said composition is a silicone-in-water emulsion and has a silicone to water weight ratio from about 1:0.4 to about 1:1.5.

2. The composition of claim 1, wherein the hydrophobic phase is substantially free of non-silicone water-immiscible substances.

3. The composition of claim 1, wherein the hydrophilic phase comprises an emulsifying agent.

4. The composition of claim 1, wherein said composition comprises a stabilizer.

5. The composition of claim 4, wherein the stabilizer is selected from formic acid, lactic acid, acetic acid, dehydroacetic acid, maleic acid, fumaric acid, citric acid, anhydrous citric acid, citric acid monohydrate, ascorbic acid, isoascorbic acid, aspartic acid, benzenesulfonic acid, edetic acid, cyclamic acid, dihydroxybenzoic acid, glutamic acid, hydrochloric acid, oleic acid, linoleic acid, capric acid, lauric acid, palmitic acid, palmitoleic acid, stearic acid and mixtures thereof.

6. The composition of claim 5, wherein the stabilizer is lactic acid.

7. The composition of claim 5, wherein the stabilizer is citric acid.

8. The composition of claim 1, wherein the hydrophilic phase further comprises one or more agents selected from thickening agents, emulsifying agents, humectants or mixtures thereof.

9. The composition of claim 1, wherein said silicone compound is selected from elastomer-10, cyclotetrasiloxane, cyclopentasiloxane, cyclohexasiloxane dimethicone, polysilicone-11, cetearyl dimethicone/vinyl dimethicone crosspolymer, dimethicone/phenyl vinyl dimethicone crosspolymer, dimethicone/vinyl dimethicone crosspolymer, cyclopentasiloxane, dimethicone crosspolymer, phenyl trimethicone, phenyl dimethicone, and mixtures thereof.

10. The composition of claim 9, wherein said silicone compound is elastomer 10.

11. The composition of claim 9, wherein said silicone compound is cyclomethicone.
12. The composition of claim 9, wherein said silicone compound is dimethicone.

13. The composition of claim 1, wherein said zinc compound is selected from zinc oxide, zinc sulfate, zinc lactate, silicone coated zinc salts and mixtures thereof.

14. The composition of claim 1, wherein said composition provides therapeutically effective concentration of benzoyl peroxide similar to that of BENZAC AC®.

15. The composition of claim 1, wherein said composition provides therapeutically effective concentration of benzoyl peroxide at least for a period of about 5 hours or up to about 12 hours in the skin layers of a subject.

16. The composition of claim 1, wherein said composition is occlusive to the skin.

17. The composition of claim 1, wherein said silicone compounds are present in an amount of from at least about 5% w/w to about 70% w/w based on the total weight of the composition.

18. The composition of claim 17, wherein said silicone compounds are present in an amount of from at least about 25% w/w to about 60% w/w based on the total weight of the composition.

19. The composition of claim 1, wherein said composition retains skin moisture by minimizing trans-epidermal water loss.

20. The composition of claim 19, wherein the average water loss is not more than about 5 g/m²h after 6 hours of topical application of the composition.

21. The composition of claim 19, wherein the trans-epidermal water loss is reduced by at least about 20% after 6 hours of topical application of the composition.

22. A method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof, comprising topically administering composition comprising benzoyl peroxide, one or more silicone compounds, and a zinc compound, wherein said method provides therapeutically effective concentration of benzoyl peroxide similar to that of BENZAC AC® in the skin layers of a subject.

23. The method of claim 22, wherein said method relates to simultaneous treatment and/or prevention of inflammatory skin disorders and related conditions thereof.
24. The method of claim 23, wherein said method relates to simultaneous treatment and/or prevention of acne and acne scars in a subject.

25. The method of claim 22, wherein said method comprises administration of the topical composition at least once daily to the subject.

26. A process of preparing a topical composition comprising a combination of benzoyl peroxide and one or more silicone compounds, wherein said process comprises: (a) preparing a hydrophilic phase comprising benzoyl peroxide; (b) preparing a hydrophobic phase comprising one or more silicone compounds; (c) adding the dispersion of step (b) to step (a); (d) filling the composition of step (c) into a suitable device, and wherein said process is a temperature-controlled process and comprises intermittent homogenization which is carried out below about 20°C or about below 10°C.

27. The process of claim 26, wherein preparation of hydrophilic phase comprising benzoyl peroxide and emulsification of hydrophobic and hydrophilic phases involve intermittent homogenization.
FIGURE 1

Mean concentrations (µg/g)

Reference Product (5%) (BENZAC AC®)  Example-1 (benzoyl peroxide 5%)  Example-2 (benzoyl peroxide 5%)

Benzoyl Peroxide compositions

■ Benzoyl Peroxide  ■ Benzoic Acid
FIGURE 3

TEWL data of test products and blank skin

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<th>Product Name</th>
<th>Initial (prior application)</th>
<th>6 HR (after application)</th>
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<tr>
<td>Skin blank</td>
<td>7.8</td>
<td>8.1</td>
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<tr>
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<td>Example 4</td>
<td>4.4</td>
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INTERNATIONAL SEARCH REPORT

International application No. PCT/IB2016/057966

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC

A61K31/00 Version=2017.01

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K, A61Q 19/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>WO 1996012498 A2 (PROCTER &amp; GAMBLE) 02 May 1996 (02-05-1996) Examples 5-6, claims 1-10</td>
<td>1-21, 26-27</td>
</tr>
<tr>
<td>X</td>
<td>EP2319510 A1, (JOHNSON &amp; JOHNSON CONSUMER) 11 May 2011 (11-05-2011) Para 03,026,047 claims 1-7</td>
<td>1, 26</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
24-03-2017

Date of mailing of the international search report
24-03-2017

Name and mailing address of the ISA/Authorized officer
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Form PCT/ISA210 (second sheet) (January 2015)
### INTERNATIONAL SEARCH REPORT

#### Information on patent family members

**International application No.**
PCT/IB2016/057966

<table>
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Form FCT/LSA/210 (patent family annex) (January 2015)
Continuation of Claims found unsearchable (Box II)

Production of plants and animals, other than microbiological processes/schemes, rules or methods of doing business, performing purely mental acts or playing games/methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods/computer programs], which does not require an international search by the International Searching Authority in accordance with PCT Article 17 (2) (a) (i) and [Rule 39.1 (iv) ].
# INTERNATIONAL SEARCH REPORT

**International application No.**
PCT/IB2016/057966

**Bos No. II** Observations where certain claims were **found** unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 22-25
   because they relate to subject matter not required to be searched by this Authority, namely:
   The subject matter of claim 22-25 relates to a method of treating and/or preventing an inflammatory skin disorder and/or related conditions thereof, a method for treatment of the human or animal body by surgery or therapy/scientific and mathematical theories/plant or animal varieties or essentially biological processes for the

2. **☐** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.