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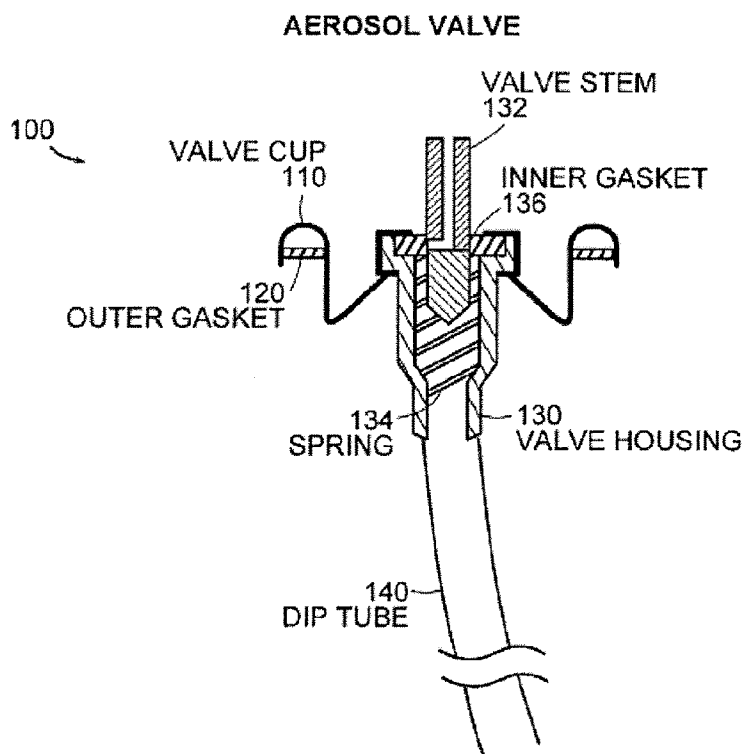
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(54) Title: **FOAM CONTAINING BENZOYL PEROXIDE**



(57) Abstract: The present invention relates to foamable compositions for treating acne comprising benzoyl peroxide; to a therapeutic kit comprising such compositions; and to a method of treating acne using such compositions.

Figure 1



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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
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Foam Containing Benzoyl Peroxide

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Application No. 61/004,838, filed on November 30, 2007, which is incorporated by reference herein in its entirety.

FIELD

[0002] The present invention relates to foamable compositions for treating inter alia acne comprising benzoyl peroxide; to a therapeutic kit comprising such compositions; and to a method of treating acne using such compositions.

BACKGROUND

[0003] Acne Vulgaris is an inflammatory disease of the skin, caused by changes in the pilosebaceous units (skin structures consisting of a hair follicle and its associated sebaceous gland). Acne develops as a result of blockages in follicles. Hyperkeratinization and formation of a plug of keratin and sebum (a microcomedo) is the earliest change. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen (DHEA-S) production at adrenarche. The microcomedo may enlarge to form an open comedo (blackhead) or closed comedo (whitehead). In these conditions the naturally occurring largely commensal bacteria *Propionibacterium acnes* can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedo, which results in redness and may result in scarring or hyperpigmentation. See, e.g., Webster GF (2002), "Acne vulgaris," *BMJ* **325** (7362): 475-9, PMID 12202330.

[0004] Benzoyl peroxide ("BPO") has been widely used for the treatment of acne. Gel or cream containing benzoyl peroxide is usually rubbed into the pores over the affected region. In addition to its therapeutic effect as a keratolytic (a chemical that dissolves the keratin plugging the pores), benzoyl peroxide also prevents new lesions by killing *P.acnes*. Benzoyl peroxide has the advantage of

being a strong oxidizer and thus does not appear to generate bacterial resistance. However, the disadvantage associated with the use of benzoyl peroxide is that it routinely causes dryness, local irritation and redness.

[0005] Additionally, compositions containing benzoyl peroxide for topical treatment of acne are available primarily in cream, lotion gel and ointment forms. Rubbing creams or ointments into the skin is inherently inefficient and difficult to achieve a constant and balanced application over large area of skin. Lotions on the other hand are not ideal as they can run and drip and may not be homogenous. Therefore, while semi-solid compositions, such as creams, gels and ointments are commonly used by consumers, new forms are desirable in order to achieve better control of the application, while maintaining or bestowing the skin beneficial properties of such products. Hence, the development of new compositions, having breakable foam consistency when released from a container and liquid properties when applied onto the skin is advantageous. Further, the development of new foamable compositions that can reduce or diminish the dryness and irritation associated with the use of benzoyl peroxide is especially desirable. Benzoyl peroxide is a sensitive active agent which reacts readily and degrades for example in oil. As a powerful oxidant, it can cause the breakdown of other active agents such as certain antibiotics if present in the same formulation and is itself sensitive to formulation conditions which have different values. Hence, there is a need to provide foamable compositions in which benzoyl peroxide is stable in the presence of other excipients.

[0006] Whilst it may be predictable to add a moisturizing agent to a BPO formulation to counter the drying effect of BPO this per se is not sufficient to prevent dryness. Identifying formulations in which BPO remains stable and homogenous that are able to improve skin moisture rapidly and effectively on application to the skin is a challenge.

[0007] Foams and, in particular, foam emulsions are complex dispersion systems which do not form under all circumstances. Slight shifts in foam emulsion composition, such as by the addition of active ingredients, may destabilize the foam. Foams are very complex and sensitive systems and are not formed at will.

Mere addition of basic ingredients like oil, water, surfactant and propellant is far from sufficient to produce foams of quality that are homogenous, stable, breakable upon mechanical force and can be used to provide a shelf stable pharmaceutical or cosmetic composition. Small deviations may lead to foam collapse. Much consideration needs to be given to facilitate the introduction of an active agent, such as examining compatibility and non reactivity with the various excipients and container and determining shelf life chemical stability.

[0008] Neubourg (US 2006/0099151), for example, notes that the stability of foam is strongly dependent on the specific composition of the foam forming components, so that even small deviations in the composition may lead to a collapse of the foam. Gordon et al. (US 3,456,052). also teaches that one cannot generate a good quality foam by simply adding a propellant to a mixture of components:

SUMMARY

[0009] In one aspect, a foamable composition for treating acne is provided, comprising (a) a prefoam emulsion composition comprising: i. benzoyl peroxide; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; and iv. water; (b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a viscosity of the prefoam composition of less than about 8000 centipoises (cps) at room temperature; and (c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature. In one embodiment, the foam produced from the foamable composition has an average bubble size of less than about 150 microns.

[0010] In one embodiment, the prefoam emulsion composition further comprises a pH adjusting component selected from the group consisting of, a base or a buffer system, said pH adjusting component selected to be able to gel the polymeric additive. In another embodiment, the pH of the prefoam emulsion composition is between about 4.0 and about 6.0. In another embodiment, the

buffer system is at a pH less than the pH of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion. In another embodiment, the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.

[0011] In one embodiment, the composition further comprises about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA). In another embodiment, the composition further comprises about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil. In another embodiment, the moisturizing complex has at least three of the following characteristics: (a) improves the chemical stability of BPO in the composition; (b) improves the homogeneity of BPO in the composition; (c) improves the quality of the foam produced from the foamable propellant composition; (d) improves the hydration of skin after 7 hours by at least about 20%.

[0012] In one embodiment, the composition further comprises about 1% glycerol stearate and one of about 1% stearyl alcohol or about 1% cetostearyl alcohol.

[0013] In one embodiment, the polymeric additive comprises an amphiphilic polymer. In another embodiment, the amphiphilic polymeric additive comprises a carbomer. In another embodiment, the polymeric additive further comprises a polymeric agent selected from the group consisting of methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (Methocel), hydroxyethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose, Sodium CMC, carboxymethylhydroxyethylcellulose, xanthan gum, guar gum, carrageenin gum, locust bean gum and tragacanth gum and mixtures of two or more thereof.

[0014] In one embodiment, the concentration range of benzoyl peroxide is selected from the group of (i) between about 0.005% and about 0.5%; (ii) between about 0.5% and about 2%; (iii) between about 2% and about 5%; (iv) between about 5% and about 10%; and (v) between about 10% and about 15%.

[0015] In one embodiment, the concentration of the one or more surface-active agents is between about 0.1% and about 5%. In another embodiment, the surface-active agent is selected from the group consisting of Steareth-21, Steareth-2, steareth 20, Polysorbate 80, Polysorbate 60, Polysorbate 20, ceteth 20, PEG 40-stearate, PEG 100-stearate, PEG-30 dipolyhydroxystearate, sorbitan stearate (span 60), sorbitan palmitate (span 40), sorbitan laurate (span 20), sorbitan monooleate (span 80), glycerol monostearate, glyceryl stearate, laureth 4, cetareth 20, macrogol cetostearyl ether, ceteth 2 (Lipocol C-2), sucrose distearate (Sisterna SP30), polyoxyethylene (100) stearate, and mixtures thereof.

[0016] In one embodiment, the composition comprises about 1% to about 15% by weight of an oil. In another embodiment, the composition comprises about 1% to about 15% by weight of an oil, wherein the oil is selected from the group consisting of mineral oil, silicone oil, jojoba oil, MCT oil and mixtures of two or more thereof.

[0017] In one embodiment, the composition comprises about 0.1% to about 5% by weight of a therapeutically active foam adjuvant selected from the group consisting of fatty alcohols having 15 or more carbons in their carbon chain; fatty acids having 16 or more carbons in their carbon chain; fatty alcohols derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; fatty alcohols having at least one double bond; fatty acids having at least one double bond; branched fatty alcohols; branched fatty acids; fatty acids substituted with a hydroxyl group; cetyl alcohol; stearyl alcohol; arachidyl alcohol; behenyl alcohol; 1-triacontanol; hexadecanoic acid; stearic acid; arachidic acid; behenic acid; octacosanoic acid; 12-hydroxy stearic acid and mixtures thereof. In another embodiment, the composition comprises at least one additional therapeutic agent, which is an antibiotic agent, selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, lincomycin class, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial

agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof, and naturally occurring antibiotic compounds. In one embodiment, the antibiotic is clindamycin.

[0018] In another aspect, a foamable composition for treating acne is provided, comprising: (a) a prefoam emulsion composition comprising: i. benzoyl peroxide; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; iv. about 5% to about 15% by weight of the total composition of a moisturizing complex; and v. water; (b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a prefoam composition that is fluid at room temperature; and (c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the foamable propellant composition is fluid at room temperature. In one embodiment, the foam produced from the foamable propellant composition has an average bubble size of less than about 150 microns.

[0019] In one embodiment, the prefoam emulsion composition further comprises a pH adjusting component selected from the group consisting of a base or a buffer system, said pH adjusting component selected to be able to gel the polymeric additive. In one embodiment, the pH of the prefoam emulsion composition is between about 4.0 and about 6.0. In another embodiment, the buffer system is at a pH less than the pH of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion.

[0020] In another aspect, a method of treating acne is provided, the method comprising administering topically to a subject having acne a foamable composition provided herein.

[0021] In another aspect, a foamable composition is provided, comprising: (a) a prefoam composition comprising: i. a suspended solid active agent; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; iv. up to about 2% by weight of the total composition of a buffer system; and v. water, wherein the viscosity of the prefoam composition is less than about 8000 centipoises (cps) at room

temperature; and (b) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature.

[0022] In another aspect, a foamable composition is provided, comprising: (a) a prefoam composition comprising: i. a suspended solid active agent; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; iv. about 5% to about 15% by weight of the total composition of a moisturizing complex; and v. water; (b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a prefoam composition that is fluid at room temperature; and (c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the foamable propellant composition is fluid at room temperature.

[0023] In one embodiment, the foam produced from the foamable propellant composition has an average bubble size of less than about 150 microns.

[0024] In one embodiment, the suspended solid agent has an average particle size of less than about 35 microns.

[0025] In one embodiment, the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.

[0026] In one embodiment, the composition further comprises about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA). In another embodiment, the composition further comprises about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.

[0027] In one embodiment, the composition further comprises at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an organic polar solvent, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight. In another embodiment, the

at least one organic carrier is present in an amount selected from the group consisting of (i) about 2% to about 5%; (ii) about 5% to about 10%; (iii) about 10% to about 20%; and (iv) about 20% to about 50% by weight.

[0028] In one embodiment, the composition further comprises a penetration enhancer. In another embodiment, the penetration enhancer is selected from the group consisting of propylene glycol, butylene glycols, hexylene glycol, glycerol, pentaerythritol, sorbitol, mannitol, oligosaccharides, dimethyl isosorbide, monooleate of ethoxylated glycerides having about 8 to 10 ethylene oxide units, polyethylene glycol 200-600, transcitol, glycofurool and cyclodextrins.

[0029] In one embodiment, the composition further comprises at least one additional therapeutic agent selected from the group consisting of an a steroidal anti-inflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an androgen, an estrogen, a prostaglandin, an antiandrogen agent, a testosterone inhibitor, a dihydrotestosterone inhibitor, an antifungal agent, an antiviral agent, an antiparasitic agent, a retinoid, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, a keratolytic agent, urea, a urea derivative, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebamic acid, adipic acid, fumaric acid, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, benzoyl chloride, calcium hypochlorite, magnesium hypochlorite, an anti-wrinkle agent, a radical scavenger, a metal, silver, a metal oxide, titanium dioxide, zinc oxide, zirconium oxide, iron oxide, silicone oxide, an organo-metallic compound, and organo-boron compound, an organo-berrilium compound, talc, carbon, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof. In another embodiment, the additional therapeutic agent is sensitive to oxidation and wherein the composition

includes a stabilizing agent which acts as an effective barrier to the possible degradative interaction of the peroxide and the additional therapeutic agent.

[0030] In one embodiment, the surface active agent comprises about 0.1% to about 5% by weight of a mixture of Glyceryl monostearate and PEG-40 Stearate.

[0031] In one embodiment, the composition about 1% to about 25% by weight of a polar solvent. In another embodiment, the polar solvent is selected from polyols, glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, sulfoxides, dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, acetamide oleates, triolein; various alkanolic acids, caprylic acid; lactam compounds, azone; alkanols, dialkylamino acetates, and admixtures thereof. In another embodiment, the polar solvent is selected from polyethylene glycol (PEG), PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD), PEG 4000, PEG 6000, PEG 10000 and mixtures thereof.

[0032] In another aspect, provided herein is a therapeutic kit to provide a safe and effective dosage for treating acne, including an aerosol packaging assembly comprising: (a) a container accommodating a pressurized product; and (b) an outlet capable of releasing the pressurized product as a foam; wherein the pressurized product comprises a foamable composition provided herein. In one embodiment, upon release from the container, a shear-sensitive foam, having a density range selected from (1) between about 0.02 g/mL and about 0.1 g/mL; and (2) between about 0.02 g/mL and about 0.1 g/mL, is produced.

[0033] In another aspect, provided herein is a therapeutic kit to provide a safe and effective dosage for treating acne, including an aerosol packaging assembly

comprising: (a) a first container accommodating a first pressurized product; (b) a second container accommodating a second pressurized product and (b) at least one outlet capable of releasing the first pressurized product and the second pressurized product as a foam; wherein the first pressurized product comprises a foamable composition provided herein, and the second pressurized product comprises a foamable composition containing one additional therapeutic agent. In one embodiment, the additional therapeutic agent is selected from antibiotics, retinoids, keratolytics and azelaic acid (AZA). In another embodiment, the additional therapeutic agent is an antibiotic selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof and naturally occurring antibiotic compounds. In another embodiment, the additional therapeutic agent is clindamycin.

[0034] In another aspect, provided herein is a method of enhancing the stability of a foamable composition comprising benzoyl peroxide for treating acne, the method comprising adding a moisturizing complex to the foamable composition. In one embodiment, the moisturizing complex comprises about 5% to about 15% by weight of the total composition. In another embodiment, the moisturizing complex comprises glycerin and sodium PCA. In another embodiment, the moisturizing complex includes an oil and comprises about 5% to about 30% by weight of the total composition and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.

[0035] In another aspect, provided herein is a method of reducing the dryness, irritation, or both associated with the use of a foamable composition containing benzoyl peroxide for treating acne, the method comprising adding a moisturizing complex to the foamable composition. In one embodiment, the moisturizing

complex comprises about 5% to about 15% by weight of the total composition. In another embodiment, the moisturizing complex comprises glycerin and sodium PCA. In another embodiment, the moisturizing complex includes an oil and comprises about 5% to about 30% by weight of the total composition and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.

[0036] In another aspect, provided herein is a method of making a foamable composition comprising containing a suspended solid active agent, comprising: (a) forming a prefoam emulsion comprising a solid active agent, one or more surface-active agents; about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; a pH adjusting component selected to be able to gel the polymeric additive; about 5% to about 15% by weight of the total composition of a moisturizing complex; and water, wherein the aqueous phase has a thickness sufficient to suspend the active agent; (b) adding a buffer system to the prefoam emulsion to reduce the viscosity of the prefoam formulation, said buffer system at a pH that is less than that of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion.; and (c) introducing a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition to the reduced viscosity prefoam emulsion to obtain a foamable composition having a stable suspended active solid and that is fluid at room temperature. In one embodiment, the prefoam emulsion has a pH in the range for 4 to 6. In another embodiment, the prefoam emulsion has a pH of less than about 5. In another embodiment, the foam produced from the foamable composition has an average bubble size of less than about 150 microns.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The invention is described with reference to the figures which are presented for the purpose of illustration and are not intended to be limiting.

[0038] FIG. 1 is a schematic illustration of an aerosol valve suitable for use in the aerosol packaging assembly according to in one or more embodiments.

[0039] FIG. 2 is a cross sectional view of an apparatus for substantially contemporaneously releasing, mixing and/or combining at least two foamable compositions measure of content from at least two containers.

[0040] FIG. 3 shows Corneometer average values after treatment of skin using foamable compositions.

[0041] FIG. 4 shows Corneometer average values after treatment of skin using foamable compositions.

[0042] FIG. 5 shows Corneometer average values after treatment of skin using foamable compositions.

[0043] FIG. 6 shows Corneometer average values after treatment of skin using foamable compositions with and without carbomer.

[0044] FIG. 7 shows Corneometer average values after treatment of skin using foamable compositions with and without carbomer.

[0045] FIG. 8 shows Corneometer average values after treatment of skin using foamable compositions with various moisturizing complexes.

[0046] FIG. 9 shows Corneometer average values after treatment of skin using foamable compositions with various moisturizing complexes.

[0047] FIG. 10 shows Corneometer average values after treatment of skin using foamable compositions with various moisturizing complexes.

[0048] FIG. 11 shows stability measurements of BPO at 30C.

[0049] FIG. 12 shows formulations each comprising a different polymer.

[0050] FIG. 13 shows formulations each comprising a different propellant.

[0051] FIG. 14 shows formulations before and after addition of citrate buffer.

[0052] FIG. 15 shows formulations comprising propellant with and without carbomer.

DETAILED DESCRIPTION

[0053] The present invention provides a foamable composition for treating acne comprising benzoyl peroxide; a therapeutic kit comprising such composition; and a method of treating acne using such composition.

Pharmaceutical Composition

[0054] All % values are provided on a weight (w/w) basis.

[0055] Benzoyl peroxide ("BPO") is commercially available or can be prepared by interaction of benzoyl chloride and a cooled solution of sodium peroxide. For laboratory procedures, see, e.g, A.I. Vogel, *Practical Organic Chemistry* (Longmans, London, 3rd ed., 1954) p 807; Gattermann-Wieland, *Praxis des organischen Chemikers* (de Gruyter, Berlin, 40th ed., 1961) p 115.

[0056] BPO is commonly used for one or more of the following indications acne (main indication), fungal skin infections and decubitus or stasis ulcers. It may also be of effect in alopecia areata, in progressive macular hypomelanosis (in combination with clindamycin and UVA), and in seborrheic keratoses.

[0057] BPO can also be used in combination with antibiotics. A non limiting list of antibiotics includes clindamycin phosphate, erythromycin, clindamycin, and erythromycin estolate.

[0058] BPO can also be used in combination with with other drugs A non limiting list of combinations is as follows: BPO + urea; BPO + sodium hyaluronate; BPO + potassium hydroxyquinoline sulfate; BPO + hydrocortisone; BPO + sulphur; BPO + cetylpyridinium chloride; BPO + miconazole nitrate; BPO + potassium hydroxyquinoline sulfate +hydrocortisone; BPO + silver + kaolin + calcium gluconate (Katoxyn); It may also be effective as BPO + adapalene; and BPO + allylamine.

[0059] It is preferable to have an average particle size of less than about 35 microns, more preferably less than about 25 microns. In the Examples described herein the formulations are homogenized resulting in an average BPO particle size distribution of about 2 to about 24 microns, The particle size is determined by light microscope in which the level of detection is about 1 micron. Thus, particles

may be present below the level of detection. The particle size can depend on one or more of, the formulation, homogenization time and quality of homogenization. The homogenizer used is a Silverson L4RT.

Foam Formulations, Breakable Foam and BPO

[0060] The term “foam” is a general term that encompasses a range of substances. Accordingly, the context in which “foam” is discussed must be examined carefully. The type and quality of the foam is of critical importance. There are many different types of foams and within each foam type there are many levels of qualities. For example, the froth on the head of beer, lather of shampoo, and lather of shaving cream have been loosely described as foam but all are different from one another. At one end of the cosmetic or pharmaceutical foam spectrum the foam can be long lasting and essentially not readily breakable like shaving foams. At the other end of the spectrum the foam can be quick breaking and collapses upon release.

Thermolabile foams are an example of type of quick breaking foam. They can contain significant amounts of thermolabile substances that aid their collapse upon being exposed to an increased temperature for example when applied to a body surface at 37C. Upon being exposed to the higher temperature they collapse rapidly. Examples are foam formulations that comprise significant amounts of volatile solvents.

[0061] Breakable foam is a specialized type of foam. It is a low density foam that is stable on release at least in the short time span of several minutes, which facilitates application to a target area; but can break readily upon the application of shear force such as gentle rubbing to spread easily over a target surface. It is not thermolabile (and does not melt at skin temperature) and nor does it display late or long delayed expansion over minutes.

[0062] Some foams expand slowly whilst others do so quickly. Some foams foam immediately and some demonstrate delayed foaming. Some require mechanical lathering and some expulsion by propellant. Whilst they all fall under

the so called term “foam” and may appear to have some common ingredients the results and properties of these products are different.

[0063] A suitable foamable formulation for a particular application may present challenges at several levels. For example, a foam formulation may require a stable pre foam formulation; a stable pre foam propellant formulation and ultimately deliverly an effective measured amount of active agent to a target. Each of these objectives poses its own unuquie challenges.

[0064] The pharmaceutical and cosmetic foams discussed herein are generated in general terms by manufacturing a suitable foamable carrier composition and loading the carrier in a pressurized valved canister with an appropriate propellant. Upon expelling the canister contents a foam can be released. The type, nature and quality of the foam depends inter alia on the carrier composition, the active agent, the propellant and the method of manufacture and storage. Making a stable (physically and chemically) formulation that can be stored in a canister with a propellant that remains stable and can produce a breakable foam of quality on release is far from trivial.

[0065] An additional difficulty frequently encountered with propellant foams is their inability to dispense a uniform application of the medically active ingredient throughout the use of the entire aerosol container. This is particularly due to the fact that the active material is not stably dispersed in the foamable composition so that it will have a tendency to settle to the bottom. Further, the dispersed material will sometimes clog the spray dispensing valve to further interfere with the uniform dispensing of the medicament.

[0066] The foamable composition carries BPO as solid particles in suspension and upon discharge from an aerosol container forms a breakable foam, which is rich and creamy in appearance, and shows very fine bubble structure. The foam does not break down immediately upon discharge, neither does it break down upon exposure to skin temperature. However, it collapses to spread easily and deposits BPO uniformly onto a skin area upon slight rubbing. The composition is able to hold BPO physically and chemically stable despite the

fact it is of low viscosity. The composition is further able to ameliorate the irritating and drying effects of BPO and actually improves skin moisture.

[0067] BPO is an insoluble solid. It has a tendency to cake or form lumps and to sediment, which could make the product non-uniform. It is a skin irritant, and its irritation potential is concentration-dependent. It dries the skin.

[0068] In order to formulate BPO in an emulsion comprising oil droplets in water the BPO emulsion must be stabilized to prevent phase separation. Simultaneously, in order to formulate BPO as a homogenous suspension the BPO emulsion must be stabilized to prevent sedimentation and also to prevent caking at the bottom of the container or BPO aggregates. Stabilization is dependent inter alia upon counteracting repellant molecular forces, particle motion and gravity.

[0069] A method of trying to achieve these objectives is to create a formulation in which the viscosity is increased to a level (high) such that the emulsion oil globules and also the suspended BPO particles have a reduced level (low) of mobility. In practical terms this means that at the viscosity range in which a BPO emulsion formulation is determined as aforesaid to have low mobility the formulation is substantially not flowable because of the high viscosity required to achieve low mobility. This may be fine for creams and ointments but it creates a unique challenge in trying to achieve breakable foams of quality. Simply adding a miscible liquid propellant to a viscous cream or ointment - putting to one side for a moment that merely adding propellant to a cream or ointment will not of itself achieve a breakable foam of quality - the addition of propellant will cause the formulation to become diluted and the viscosity reduced. In turn the BPO will have a higher motion and be more likely to cake and to sediment and in turn the emulsion formulation will be more vulnerable to phase separation.

[0070] As can be appreciated from the above discussion, forming a homogeneous suspension of a BPO foamable formulation using an emulsion formulation with high viscosity – so that even after addition of propellant the formulation has high viscosity - in order to try and stabilize the oil droplets and BPO particles, minimize molecular motion and discourage gravitational sedimentation in the canister in which the formulation is stored simply will not do

for foamable compositions. Such high viscous formulations are not desirable for foamable compositions since they have low flowability and may exhibit one or more of the following: are not shakable; form a block, i.e., a solid no flowable mass, in the canister; do not result in uniform expulsion; and if expelled may be accompanied by unwanted phenomena such as one or more of jets, tailing and noise.

[0071] Unexpectedly it has been surprisingly discovered that it is possible to make compositions which are truly flowable and have low viscosity in which the propellant forms part of the oil phase of the emulsion formulation but nevertheless surprisingly does not make the formulation substantially vulnerable to phase separation and or sedimentation. Moreover these compositions are stable and are able to form breakable foam of quality that spreads easily and is able to deliver an effective and measurable amount of active agent homogeneously to a target surface.

[0072] One key element is the polymeric agent used in the formulation. The polymeric agent can contribute to the stability and stabilization of the formulation. Concentrations of polymeric agents and other thickeners have in the past been used to achieve very high viscosities of at least 20,000 centipoises (cps) to a million or more cps. Surprisingly, it has been unexpectedly found that by using low viscosities of the order of about 7000 to about 8000 cps or less for the pre-foam formulation whose viscosity is further reduced upon inclusion of propellant it has been possible to achieve a stable BPO formulation that produces breakable (non thermolabile) foam of good quality even after addition of propellant and even though the foamable formulation with propellant is fluid and easily shakable. In a preferred embodiment the viscosity of a formulation comprising propellant is below about 5000 cps and in a more preferred embodiment it is below about 3000 cps. At such low levels of viscosity, one would expect a suspended solid active agent such as BPO to precipitate out of solution. In the low viscosity formulations provided herein, BPO unexpectedly remains homogeneously dispersed in suspension. For pharmaceutical applications, BPO needs to be homogeneous to ensure that the amount of BPO in the first dose and the last dose.

[0073] An important factor in the use of a polymeric agent is to ensure the polymer(s) is appropriately and correctly swelled in the presence of water by adding an effective amount of base. Without being bound by any theory it may be the case that the lower levels of polymeric agent still form a semi water gel like infrastructure that unexpectedly is able to stabilize the BPO physically and chemically at low viscosities.

[0074] In an embodiment the polymer is an amphiphilic polymer, such as, an acrylates/C10-30 alkyl acrylate crosspolymer. The hydrophilic and hydrophobic regions of these polymers serve to interact with and stabilize hydrophilic and lipophilic components, respectively, of a composition. In one embodiment the polymeric agent is a carbomer.

[0075] By way of example, suitable polymeric surfactants include cross linked copolymers of acrylic acid and a hydrophobic comonomer, such as Pemulen TR-1 and Pemulen TR-2, ETD 2020 and Carbopol 1382 (all, Acrylates/C10-30 alkyl acrylate crosspolymer), Natrosol CS Plus 330 and 430 and Polysurf 67 (all, cetyl hydroxyethyl cellulose), Aculyn 22 (acrylates /steareth-20 methacrylate copolymer), Aculyn 25 (acrylates/ laureth-25 methacrylate copolymer), Aculyn 28 (acrylates /beheneth-25 methacrylate copolymer), Aculyn 46 (PEG-150/stearyl alcohol/SMDI copolymer), Stabylen 30 (acrylates/vinyl isodecanoate), Structure 2001 (acrylates/steareth-20 itaconate copolymer), Structure 3001 (acrylates/ceteth-20 itaconate copolymer) and Structure Plus (acrylates/aminoacrylates/C10-30 alkyl PEG 20 itaconate copolymer), where PEG is polyethylene glycol, PPG is polypropylene glycol.

[0076] Other exemplary amphiphilic copolymers include silicone polymers such as amphiphilic silicone polyols or copolyol, for example cetyl dimethicon copolyol and dimethicone copolyol PPG-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starches, and amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol (also known as "poloxamer").

[0077] The gelling agent may include other types of gelling agents, in combination with an amphiphilic copolymer. A non limiting list of other types such as water soluble cellulose, or gums like guar and xanthan is provided below.

[0078] On comparing different polymers and combinations of polymers it was noted that whilst formulations with non ampiphilic polymers like methocel and xanthan produced homogenous BPO formulations, nevertheless such formulations separated over time albeit reversibly such that homogeneity was seen to be restored on shaking. In contrast these formulations with the addition of relatively low levels of ampiphilic polymer carbopol were found to be homogenous over time.

[0079] The comparative analysis of Example 24 showed that carbapol was better than pemulen was better than xanthan. It is difficult to try and explain why in a fluid hydrocarbon low viscosity medium one polymer is better than another. Moreover, it is completely unexpected that in a fluid viscous emulsion medium carbopol can hold the BPO in a homogenous distribution even after six months.

[0080] A further element and aid to reducing viscosity in the presense of gelling agents is the use of a buffer or buffer complex. It was observed that when small amounts of citrate buffer or alternatively lactate buffer was added to the carbomer gel it results in a viscous liquid. Thus, the presence of citrate or lactate buffer was noted to cause a thick emulsion gel or paste containing carbomer to become fluid. Other similar buffers may work. Non limiting examples of appropriate possible buffers, which may achieve the same objective are acetate, malate, sorbate, succinate and tartrate. As is explained below and as is seen in the Examples when the acid of the buffer is added first this alone can break the gel. Thus, in one or more embodiments when a buffer is added it is added sequentially. In other embodiments it is added simultaneously as a stock solution. In further embodiments a pH adjuster is added.

[0081] A further element and complication is that in certain circumstances it has been observed that the propellant itself can cause the BPO to chemically degrade. Therefore it is not sufficient to merely dilute the formulation with propellant but the formulation must also be formulated such that the BPO remains substantially un-degraded following application of propellant and its absorption into the oil phase of the emulsion.

[0082] According to one aspect, a foamable composition is provided for treating acne comprising: (a) a prefoam emulsion composition comprising: i. benzoyl peroxide; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; and iv. water; (b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a viscosity of the prefoam composition of less than about 8000 centipoises (cps) at room temperature; and (c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature. In one embodiment, the foam produced from the foamable composition has an average bubble size of less than about 150 microns.

[0083] In certain embodiments, the composition further comprises about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA). In some cases, the composition further comprises about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil. In other embodiments, the moisturizing complex has at least three of the following characteristics: (a) improves the chemical stability of BPO in the composition; (b) improves the homogeneity of BPO in the composition; (c) improves the quality of the foam produced from the foamable propellant composition; (d) improves the hydration of skin after 7 hours by at least about 20%.

[0084] In certain embodiments, the composition described hereinabove may further comprise at least one organic carrier at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an organic polar solvent, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight. In some cases, the at least one organic carrier is present in an amount selected from the group consisting of (i) about 2% to about 5%; (ii) about 5% to about 10%; (iii) about 10% to about 20%; and (iv) about 20% to about 50% by weight.

[0085] In certain embodiments, the composition described hereinabove may further comprise about 0.1% to about 5% by weight of a therapeutically active foam adjuvant is selected from the group consisting of fatty alcohols having 15 or more carbons in their carbon chain; fatty acids having 16 or more carbons in their carbon chain; fatty alcohols derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; fatty alcohols having at least one double bond; fatty acids having at least one double bond; branched fatty alcohols; branched fatty acids; fatty acids substituted with a hydroxyl group; cetyl alcohol; stearyl alcohol; arachidyl alcohol; behenyl alcohol; 1-triacontanol; hexadecanoic acid; stearic acid; arachidic acid; behenic acid; octacosanoic acid; 12-hydroxy stearic acid and mixtures thereof.

[0086] In other embodiments, the composition comprises at least one additional therapeutic agent, which is an antibiotic agent, selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, lincomycin class, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof, and naturally occurring antibiotic compounds. In one embodiment, the antibiotic is clindamycin.

[0087] In certain embodiments, the concentration range of benzoyl peroxide is selected from the group of (i) between about 0.005% and about 0.5%; (ii) between about 0.5% and about 2%; (iii) between about 2% and about 5%; (iv) between about 5% and about 10%; and (v) between about 10% and about 15%. In certain other embodiments, the concentration of the surface-active agent is between about 0.1% and about 5%.

[0088] In another aspect, a foamable composition is provided, comprising: (a) a prefoam composition comprising: i. a suspended solid active agent; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total

composition of at least one polymeric additive; iv. up to about 2% by weight of the total composition of a buffer system; and v. water, wherein the viscosity of the prefoam composition is less than about 8000 centipoises (cps) at room temperature; and (b) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature.

In another aspect, a foamable composition is provided, comprising: (a) a prefoam composition comprising: i. a suspended solid active agent; ii. one or more surface-active agents; iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; iv. about 5% to about 15% by weight of the total composition of a moisturizing complex; and v. water; (b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a prefoam composition that is fluid at room temperature; and (c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the foamable propellant composition is fluid at room temperature.

[0089] In one embodiment, the foam produced from the foamable propellant composition has an average bubble size of less than about 150 microns.

[0090] In one embodiment, the suspended solid agent has an average particle size of less than about 35 microns.

[0091] In one embodiment, the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.

[0092] In one embodiment, the composition further comprises about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA). In another embodiment, the composition further comprises about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.

[0093] In certain embodiments, the polymeric agent includes, but not limited to, a water-soluble polymer, a water-insoluble polymer, a gelling agent, an inorganic gelling agent, a mucoadhesive macromolecule and a film forming polymer. In certain other embodiments, the water-soluble polymer includes, but not limited to, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (Methocel), hydroxyethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose, carboxymethylhydroxyethylcellulose, xanthan gum, guar gum, carrageenin gum, locust bean gum and tragacanth gum.

[0094] In one embodiment, the polymeric additive comprises an amphiphilic polymer. In another embodiment, the amphiphilic polymeric additive comprises a carbomer. In another embodiment, the polymeric additive further comprises a polymeric agent selected from the group consisting of methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (Methocel), hydroxyethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose, Sodium CMC, carboxymethylhydroxyethylcellulose, xanthan gum, guar gum, carrageenin gum, locust bean gum and tragacanth gum and mixtures of two or more thereof.

[0095] In certain embodiments, the composition described herein above may further contain a penetration enhancer. In some cases, the penetration enhancer includes, without limitation, propylene glycol, butylene glycols, hexylene glycol, glycerol, pentaerythritol, sorbitol, mannitol, oligosaccharides, dimethyl isosorbide, monooleate of ethoxylated glycerides having about 8 to 10 ethylene oxide units, polyethylene glycol 200-600, transcitol, glycofurool and cyclodextrins.

[0096] In certain embodiments, the composition described herein above may further contain the composition further comprises a pH adjusting agent (or a pH adjuster). In some cases, the pH adjusting agent is selected from an acid, a base and a buffering agent. In some other cases, the pH adjusting agent is selected from citric acid, sodium citrate and mixtures thereof. In certain embodiments, the pH of the foamable composition is between about 3.0 and about 7.0, for example, about 3.0, about 3.5, about 4.0, about 4.5, about 5.0, about 5.5, about 6.0, about 6.5 and about 7.0. In certain other embodiments, the pH of the foamable

composition is between about 3.0 and about 6.0. In certain other embodiments, the pH of the foamable composition is between about 4.0 and about 7.0. In certain other embodiments, the pH of the foamable composition is between about 4.0 and about 5.0.

[0097] In some embodiments, the prefoam emulsion composition further comprises a pH adjusting component selected from the group consisting of, a base or a buffer system, said pH adjusting component selected to be able to gel the polymeric additive. In other embodiments, the pH of the prefoam emulsion composition is between about 4.0 and about 6.0. In some cases, the buffer system is at a pH less than the pH of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion. In other embodiments, the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.

[0098] A pH adjuster includes buffer but a buffer does not necessarily include a pH adjuster. A pH adjuster can be, for example, an acid alone or an acidic agent alone or a base alone or a basic agent alone or a buffer. A simple buffer is a solution which resists change of pH upon addition of small amounts of acid or base, or upon dilution. It is an aqueous solution consisting of a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid. In some case the buffer can be a biological buffer such as Tris.. In the Examples herein a buffer primarily comprises an acid and its salt (for example, citric acid/sodium citrate). The buffer can be used to bring the formulation to a desired pH and is designed to maintain the pH at the desired pH so that the pH remains substantially unchanged when a composition is exposed to small amounts of acidic or basic substances. In the absence of buffer the same composition may have shown a significant pH change.

[0099] Polymeric agents used to form gels have different sensitivities to changes in pH. For example, methocel and xanthan gum are not expected to be sensitive to pH changes, whereas carbopols are sensitive to pH. Carbopols obtained from one manufacturer may have a different sensitivity range than that obtained from a different manufacturer. Thus, it is important to look at what the manufacturer says about its product. The carbopols used in the Examples

provided herein were obtained from Noveon. The pH sensitivity appears to be reversible. When buffer is added to the gel, there is a small reduction in pH but this appears to destroy the carbomer matrix and turn the gel into a liquid. In fact when the acid component of the buffer is added first this was seen to destroy the gel. As such, it is expected that addition of any acids that can reduce the pH of the formulation to below about pH 4 would have this effect. Thus, buffers can break the gel, and acids alone can also be expected to break the gel. Non-limiting examples of acids include alpha hydroxyl acid, an aliphatic beta hydroxyacid, an aromatic acid, an aromatic hydroxyl acid, an alpha ketoacid, an aliphatic carboxylic acid, a branched aliphatic carboxylic acid, a short chain carboxylic acid, a fatty acid, an omega-3 fatty acid, an omega-6 fatty acid, an omega-9 fatty acid, a dicarboxylic acid, a branched dicarboxylic acid, an unsaturated dicarboxylic acid, an amino acid and a dimer or oligomer of amino acids. For the acid to have an appropriate effect it is envisaged that it should be miscible in water. If the acid has low or poor miscibility its effect will be reduced, although incorporating it into an aqueous emulsion may help.

[0100] In one embodiment, the concentration of the one or more surface-active agents is between about 0.1% and about 5%. In another embodiment, the surface-active agent is selected from the group consisting of Steareth-21, Steareth-2, steareth 20, Polysorbate 80, Polysorbate 60, Polysorbate 20, ceteth 20, PEG 40-stearate, PEG 100-stearate, PEG-30 dipolyhydroxystearate, sorbitan stearate (span 60), sorbitan palmitate (span 40), sorbitan laurate (span 20), sorbitan monooleate (span 80), glycerol monostearate, glyceryl stearate, laureth 4, cetareth 20, macrogol cetostearyl ether, ceteth 2 (Lipocol C-2), sucrose distearate (Sisterna SP30), polyoxyethylene (100) stearate, and mixtures thereof.

[0101] In certain other embodiments, the surfactant is selected from Steareth-21, Steareth-2, Polysorbate 60, and mixtures thereof. In certain embodiments, the foam adjuvant is Stearyl alcohol. In certain other embodiments, the emollient or emulsifier is Glyceryl monostearate or PEG-40 Stearate. In certain embodiments, the gelling agent is selected from Sodium CMC, Xanthan gum, Methocel K100, and mixtures thereof. In certain other embodiments, the pH adjusting agent is present and is selected from an acid, a base and a buffering agent. In certain

embodiments, the pH adjusting agent is selected from citric acid, sodium citrate and mixtures thereof. In certain other embodiments, the moisturizing complex comprises glycerin and sodium PCA.

[0102] In certain embodiments of this aspect, the gelling agent is selected from acrylates/C10-30 alkyl acrylate crosspolymer, a carbomer, xanthan, Methocel (hydroxypropyl methyl cellulose), sodium carboxymethylcellulose ("CMC"), Klucel (hydroxypropylcellulose) and mixtures thereof. According to various embodiments the agent or mixtures thereof are selected to achieve a viscosity of less than about 8000cps, which is preferably less than 6000 cps and more preferably less than about 3000 cps after addition of propellant.

[0103] In certain embodiments of this aspect, the surfactant is selected from Polysorbate 60, Polysorbate 20, sorbitan laurate (span 20), and mixtures thereof. In certain other embodiments, the film forming agent comprises Klucel EF.

[0104] In certain embodiments of this aspect, the film forming agent comprises Klucel EF. In certain other embodiments, the oil comprises Jojoba oil. Jojoba oil (pronounced "ho-HO-bah") is the liquid wax produced in the seed of the Jojoba (*Simmondsia chinensis*) plant. Jojoba oil is a straight chain wax ester, 36 to 46 carbon atoms in length. Each molecule consists of a fatty acid and a fatty alcohol joined by an ester bond. Each molecule has two points of cis-unsaturation, both located at the 9th carbon atom from either end of the molecule. Jojoba oil comprises approximately 66-71% eicosenoic acid, 14-20% docosenoic acid and 10-13% oleic acid. Refined jojoba oil is colorless and odorless. The melting point of jojoba oil is approximately 10°C. Jojoba oil is relatively shelf-stable when compared with other vegetable oils. Unlike common vegetable oils, jojoba oil is chemically very similar to human sebum. Most jojoba oil is used as an ingredient in cosmetics and personal care products, especially skin care and hair care. Therapeutically it can aid in the healing process.

[0105] In certain embodiments of this aspect, the oil comprises silicone. Non-limiting examples of silicone include dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer. In one embodiment,

the oil is volatile. In an embodiment, the volatile silicone is cyclic, such as, cyclomethicone.

[0106] In certain embodiments of this aspect, the polar solvent is selected from polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, such as acetamide oleates such as triolein; various alkanolic acids such as caprylic acid; lactam compounds, such as azone; alkanols, such as dialkylamino acetates, and admixtures thereof.

[0107] In certain other embodiments of this aspect, the polar solvent is selected from polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof. In certain embodiments of this aspect, the polar solvent is propylene glycol. In certain embodiments, the film forming agent is Klucel EF. In certain other embodiments, the surfactant is selected from Polysorbate 60, Polysorbate 20, Ceteth 20, sorbitan laurate (span 20), PEG 100-stearate, and mixtures thereof. In certain embodiments, the the foam adjuvant comprises stearyl alcohol.

[0108] In certain embodiments of this aspect, the surfactant comprises polysorbate 60. In certain other embodiments, the foam adjuvant comprises stearyl alcohol. In some cases, the gelling agent comprises sodium CMC.

[0109] In certain embodiments, the foamable composition described hereinabove may further comprise at least one additional therapeutic agent, which

is an antibiotic agent, selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof and naturally occurring antibiotic compounds.

[0110] In certain embodiments, the additional antibiotic is an antibiotic of the lincomycin family. In one embodiment, the antibiotic is clindamycin.

[0111] In certain embodiments, the foamable composition described hereinabove may further include at least one additional therapeutic agent selected from the group consisting of an a steroidal anti-inflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an androgen, an estrogen, a prostaglandin, an antiandrogen agent, a testosterone inhibitor, a dihydrotestosterone inhibitor, an antifungal agent, an antiviral agent, an antiparasitic agent, a retinoid, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, a keratolytic agent, urea, a urea derivative, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, a allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebacic acid, adipic acid, fumaric acid, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, benzoyl chloride, calcium hypochlorite, magnesium hypochlorite, an anti-wrinkle agent, a radical scavenger, a metal, silver, a metal oxide, titanium dioxide, zinc oxide, zirconium oxide, iron oxide, silicone oxide, an organo-metallic compound, and organo-boron compound, an organo-berrilium compound, talc, carbon, an anti wrinkle agent, a skin

whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

[0112] In certain embodiments, the additional therapeutic agent is sensitive to oxidation and wherein the composition includes a stabilizing agent which acts as an effective barrier to the possible degradative interaction of the peroxide and the additional therapeutic agent.

[0113] According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. This disadvantage is particularly meaningful in the case of an antibiotic treatment, which is often directed to open wounds and damaged skin and mucosal tissues. Thus, in one or more embodiments, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

[0114] In one or more embodiments, the concentration of surface-active agent about 0.1% to about 5%, or from about 0.2% to about 2%.

Aerosol packaging assembly

[0115] The aerosol packaging assembly typically includes a container suitable for accommodating a pressurized product and an outlet capable of releasing a foam. The outlet is typically a valve. Figure 1 illustrates a typical aerosol valve 100. The valve is made up of the valve cup 110 typically constructed from tinplated steel, or aluminum, an outer gasket 120, which is the seal between the valve cup and the aerosol can (not shown), a valve housing 130, which contains the valve stem 132, spring 134 and inner gasket 136, and a dip tube 140, which allows the liquid to enter valve. The valve stem is the tap through which the product flows. The inner gasket 136 covers the aperture 150 (hole) in the valve stem. The valve spring 134 is usually made of stainless steel.

[0116] The valve stem is fitted with small apertures 150 (also termed "orifices" and "holes"), through which the product flows. Valves may contain one, two, three, four or more apertures, depending on the nature of the product to be dispensed. In the closed position, the aperture(s) is covered by the inner gasket. When the actuator is depressed it pushes the valve stem through the inner gasket, and the aperture(s) is uncovered, allowing liquid to pass through the valve and into the actuator.

[0117] The valve can have a stem with 1 to 4 apertures, or 1 to 2 apertures. Each aperture can have a diameter of about 0.2 mm to about 1 mm, or a diameter of about 0.3 mm to about 0.8 mm. The total aperture area, i.e., the sum of areas of all apertures in a given stem, is between about 0.01 mm² and 1 mm² or the total aperture area is between about 0.04 mm² and 0.5 mm².

[0118] In order to provide proper therapy, precise dosing is desired. According to one or more embodiments, the valve is attached, directly, or through a tube, to a metered dose device, which for dispensing an accurate dose of drug in the form of a foam. The metered dose valve is selected to release a foam in a volume that provides an adequate therapeutic dose to the target site of the skin, a body surface, a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum.

[0119] In one or more embodiments, the meter dose valve provides a unit dose of between about 10 µL and about 1000 µL. Assuming a representative foam density (specific gravity) of 0.06 g/mL, a 10 µL valve provides a volume of about 0.17 mL of foam, and a 1000 µL metered dose valve provides about 17 mL of foam. Thus, by selecting a specific metered dosing valve and adjusting the foam density by fine tuning formulation parameters and adjusting the ratio between the liquid components of the composition and the propellant, one can design an adequate dosage form according to the specific target site. Exemplary metered dose devices may be found in co-pending application serial no. 11/406,133, entitled "Apparatus and Method for Releasing a Measured Amount of Content from a Container," filed April 18, 2006, which is hereby incorporated in its entirety by reference.

[0120] According to one aspect, a therapeutic kit is provided to afford a safe and effective dosage for treating acne, including an aerosol packaging assembly comprising:

- (a) a container accommodating a pressurized product; and
- (b) an outlet capable of releasing the pressurized product as a foam;

wherein the pressurized product comprises a foamable composition.

[0121] In certain embodiments of this aspect, the kit produces a shear-sensitive foam having a density range selected from between about 0.02 gr/mL and about 0.1 gr/mL upon release from the container.

[0122] According to another aspect, the aerosol packaging assembly may include two containers suitable for contemporaneously mixing and/or combining two foamable compositions. In some cases, the aerosol packaging assembly comprises:

- a. a first container accommodating a first pressurized product;
- b. a second container accommodating a second pressurized product and
- c. at least one outlet capable of releasing the first pressurized product and the second pressurized product as a foam;

wherein the first pressurized product comprises a foamable composition according to claim 1, and the second pressurized product comprises a foamable composition containing one additional therapeutic agent.

[0123] In certain embodiments of this aspect, the additional therapeutic agent is selected from antibiotics, retinoids, keratolytics and azelaic acid(AZA). In certain other embodiments, the additional therapeutic agent is an antibiotic selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and

polymers thereof and naturally occurring antibiotic compounds. In some cases, the additional therapeutic agent is clindamycin.

[0124] US 2007/0069046 describes a therapeutic kit for releasing a predetermined quantity of a foamable composition from a plurality of pressurized containers, which is incorporated herein by its entirety. Figure 2 shows a kit 100 including a dispenser head engaged with a pair of pressurized containers 120, 130.

[0125] In one embodiment, FIG. 2 shows in cross-section a kit 100 including a dispenser head 110 mounted on two containers 120 and 130 containing contents 125 and 135 for dispensing and mixing. The dispenser head and the containers are accommodated in a housing. The dispenser head 110 includes a flow guide 140, which also functions as an actuator. Flow guide 140 houses a flow conduits 150, 155, whose function is described in greater detail below. The cross-sectional area of each conduit may be the same or different. The container contents include a foamable composition that is flowable, e.g., a fluid, a liquid and a semi-liquid. Container 120 has stem 128 that extends from container 120 and engages with fluid conduit at an inlet 160. Similarly, container 130 has stem 138 that extends from container 130 and engages with fluid conduit at an inlet 165.

[0126] Each container 120 or 130 in the embodiment described is of the pressurized aerosol can type and has its own internal valve (170, 175) fitted with a valve stems 128, 138, respectively. Container 120 includes a hollow tube 127 that is attached to or integrally formed with, a internal valve 170, thereby readily facilitating flow of liquids, fluids and gas through tube 127 through valve 170 and into stem 128. The stem 128 is hollow and depressing the stem opens the valve so that the container contents are dispensed through the hollow stem. Similarly, container 130 includes a hollow tube 137 that is attached to or integrally formed with, a internal valve 175, thereby readily facilitating flow of liquids, fluids and gas through tube 137 through valve 175 and into stem 138. The stem 138 is hollow and depressing the stem opens the valve so that the container contents are dispensed through the hollow stem. The valve in some types of containers

includes a return spring for returning the stem to its initial position so as to close the valve when the force depressing the stem is removed.

[0127] Flow guide 140 has a pair of flow conduits 150, 155, each defined by a tubular wall having an inlet 160, 165, respectively, and an outlet 180, 185, respectively. Inlets 160, 165 of flow conduits 150, 155 abut of the upper ends of stems 128, 138 respectively, when the containers 120, 130 are fully mounted on the dispenser head 140. When the flow conduits 150, 155 are in place in the flow guide 140, outlets 160, 165 are positioned coaxial with the respective container stems 128, 138.

[0128] The foamed material exits from outlets 180, 185, where it is combined and/or mixed. The position and location of the outlets can be adjusted to obtain the desired degree of combining and/or mixing. Because the individual foamed components do not mix inside the dispenser head, the foam is able to expand to its optimal extent. Furthermore, the outlets are positioned to achieve a reasonable, good or high degree of combination/mixing/interaction without loss or substantial loss of foam quality.

[0129] The dispenser head of the current invention is advantageous compared to the prior art dispensing apparatus, in which some mixing occurs within the apparatus and/or end nozzles attached to the apparatus, thereby resulting in contamination and/or requiring disposal of the end nozzles and/or cleaning of some or all of the apparatus.

[0130] The dispenser assembly 140 is used as follows. The user attaches appropriate containers 120, 130 onto the dispensing head. The containers may contain the some or different contents. In one or more embodiments, the contents may include a cosmetic and/or pharmaceutical carrier, and/or an active agent. The carrier may be in each of the containers, or may be obtained upon mixing of the contents of two or more containers. In one embodiment, one or more containers may include a cosmetic and/or pharmaceutical carrier and an additional container may include an active therapeutic or cosmetic agent. To start dispensing the container contents, the user activates the valve stems, causing the flow conduits 150, 155 to move down, thereby pressing the stems 128, 138

downward and opening the valves 170, 175 of containers 120, 130, respectively. In this embodiment, activation occurs by pressing on an upper surface 190 of the Flow guide to displace the flow guide towards the stems.

[0131] Alternatively, a separate member of the dispensing head may serve as the actuator, so that when the user presses against an upper surface of the dispenser, the dispenser head is displaced downwards and against the upper stems of the containers. Other levers, buttons or switches may be provided to actuate the kit.

[0132] When the actuator is at rest, stems valves 170, 175 are sealed, causing the container contents to remain in the pressurized containers 120, 130. When the actuators is activated, the stem 128, 138 are pressed downwards causing stem valves 170, 175 to open and the container contents to be released. The contents flows through stems 128, 138 to inlets 160, 165 and into flow conduits 150, 155. The contents then reaches outlets 180, 185, so as to be dispensed.

[0133] Thus, the flow guide includes a plurality of exit ducts that release foamed content from their respective containers such that the contents are substantially contemporaneously mixed and/or combined at a location external to the flow guide.

[0134] By a location external, this means at an area or space that is at a point of exit, that is at a point of reference just or somewhat beyond the point of exit or that is at a point of reference just before a point of exit (for example, the latter may apply where the ends of the exit conduits are formed at an angle).

[0135] It is also envisaged that one of the containers can be a non aerosol mechanical foamer. By way of a non-limiting example only, such a non aerosol mechanical first foamer container can include non aerosol mechanical foamers as disclosed in any of US Patent 4,018,396; US Patent 4,440,320; US Patent 4,603,812 and US Patent 4,738,396 all of which are hereby incorporated in their entirety by reference. So in an embodiment there is provided a dual canister configuration in which one of the canisters is a propellant driven system and one of the canisters is a mechanical driven system.

[0136] In an embodiment where it is intended that the canisters and head are to be operated in an inverse position, the hollow tubes 127,137 of Fig. 2 may be provided inverted substantially in the shape of a "U" wherein the inlet end of the hollow tubes 127,128 for the composition is submerged below the surface of the composition when the canister is inverted.

[0137] The dispensing head may be detachable from the canisters, or it may be permanently attached. In detachable embodiments, outlets 160, 165 abut or sealably contact container stems 128, 138, respectively. In disposable embodiments, outlets 160, 165 may be integral with container stems 128, 138, respectively.

Antibiotic Agents

[0138] In some embodiments, the composition or kit includes an active agent, such as antibiotics. In the context herein, an antibiotic agent is a substance that has the capacity to inhibit the growth of or to destroy bacteria and other microorganisms. In one or more embodiments the antibiotic agent is used in combination with BPO. Where the agent is compatible with BPO they can be presented in the same formulation in the same canister. Where the antibiotic agent destabilizes BPO then the other agent can be presented using a dual chamber delivery system or kit like that described above. Thus, in one embodiment BPO is presented in a first foamable formulation and stored in a first canister and the agent in a second foamable formulation and stored in a second canister. Upon release from the dual canister system the two foams are simultaneously expelled and can be delivered to a target site.

[0139] In one or more embodiments, the antibiotic agent is selected from the classes consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium

compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof and naturally occurring antibiotic compounds. A non limiting list of antibiotics includes clindamycin phosphate, erythromycin, clindamycin and erythromycin estolate.

[0140] Oxidizing agents and substances that release free radicals and/or active oxygen. In one or more embodiments, the antibiotic agent comprises strong oxidants and free radical liberating compounds, such as oxygen, hydrogen peroxide, elemental halogen species, as well as oxygenated halogen species, bleaching agents (e.g., sodium, calcium or magnesium hypochloride and the like), perchlorite species, iodine and iodate. Organic oxidizing agents are also included in the definition of “oxidizing agent” according to the present invention, such as quinones. Such agents possess a potent broad-spectrum activity.

[0141] Additional non-limiting examples of combinations of an antibiotic agent and an additional active agent are provided in the following table:

Disorder	Exemplary Additional Active Agent
acne	At least one agent selected from the group consisting of a retinoid; a keratolytic acid, an alpha-hydroxy acid and derivatives thereof, a beta-hydroxy acid and derivatives thereof, a skin-drying agent, an anti-seborrhea agent, a corticosteroid and a non-steroidal anti-inflammatory agent.
Rosacea	At least one agent selected from the group consisting of a retinoid; a keratolytic acid, an alpha-hydroxy acid, a beta-hydroxy acid and derivatives thereof.
Otitis	At least one agent selected from the group of an antifungal agent, a local anesthetic agent, a corticosteroid and a non-steroidal anti-inflammatory agent.
Psoriasis	At least one agent selected from the group consisting of a corticosteroid, coal tar, anthralin and a photodynamic therapy agent

Hence, in many cases, the inclusion of an additional therapeutic agent in the foamable composition, contributes to the clinical activity of the antibiotic agent. Thus, in one or more embodiments, the foamable composition further includes at least one additional therapeutic agent, in a therapeutically effective concentration.

[0142] In one or more embodiments, the at least one additional therapeutic agent is selected from the group consisting of a steroidal anti-inflammatory agent, a nonsteroidal anti-inflammatory drug, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an antifungal agent, an antiviral agent, an antiparasitic agent, a vasoactive agent, a vasoconstrictor, a vasodilator, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebacic acid, adipic acid, fumaric acid, an antibiotic agent, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, an anti-wrinkle agent, a radical scavenger, a metal oxide (e.g., titanium dioxide, zinc oxide, zirconium oxide, iron oxide), silicone oxide, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

[0143] In certain cases, the disorder to be treated involves unaesthetic lesions that need to be masked. For example, rosacea involves papules and pustules, which can be treated with an antibiotic agent, as well as erythema, telangiectasia and redness, which partially respond to treatment with an antibiotic agent. Thus, in one or more embodiments, the additional active agent is a masking agent, i.e., a pigment. Non limiting examples of suitable pigments include brown, yellow or red iron oxide or hydroxides, chromium oxides or hydroxides, titanium oxides or hydroxides, zinc oxide, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake and FD&C Yellow No. 6 aluminum lake.

[0144] The foamable composition can be an emulsion, or microemulsion, including an aqueous phase and an organic carrier phase. The organic carrier is selected from a hydrophobic organic carrier (also termed herein "hydrophobic solvent"), an emollient, a polar solvent, and a mixture thereof. The identification of a "solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a carrier in the foamable compositions described herein.

Hydrophobic Organic Carrier

[0145] A "hydrophobic organic carrier" as used herein refers to a material having solubility in distilled water at ambient temperature of less than about 1 gm per 100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL. It is liquid at ambient temperature. The identification of a hydrophobic organic carrier or "hydrophobic solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a hydrophobic carrier in the foamable compositions described herein.

[0146] In one or more embodiments, the hydrophobic organic carrier is an oil, such as mineral oil. Mineral oil (Chemical Abstracts Service Registry number 8012-95-1) is a mixture of aliphatic, naphthalenic, and aromatic liquid hydrocarbons that derive from petroleum. It is typically liquid; its viscosity is in the range of between about 35 CST and about 100 CST (at 40°C), and its pour point (the lowest temperature at which an oil can be handled without excessive amounts of wax crystals forming so preventing flow) is below 0°C. The hydrophobic organic carrier does not include thick or semi-solid materials, such as white petrolatum, also termed "Vaseline", which, in certain compositions is disadvantageous due to its waxy nature and semi-solid texture.

[0147] According to one or more embodiments, hydrophobic solvents are liquid oils originating from vegetable, marine or animal sources. Suitable liquid oil includes saturated, unsaturated or polyunsaturated oils. By way of example, the unsaturated oil may be olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils or mixtures thereof, in any proportion.

[0148] Suitable hydrophobic solvents also include polyunsaturated oils containing poly-unsaturated fatty acids. In one or more embodiments, the unsaturated fatty acids are selected from the group of omega-3 and omega-6 fatty acids. Examples of such polyunsaturated fatty acids are linoleic and linolenic acid, gamma-linoleic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Such unsaturated fatty acids are known for their skin-conditioning effect, which contribute to the therapeutic benefit of the present foamable composition. Thus, the hydrophobic solvent can include at least 6% of an oil selected from omega-3 oil, omega-6 oil, and mixtures thereof. In the context herein, oils that possess therapeutically beneficial properties are termed "therapeutically active oil".

[0149] Another class of hydrophobic solvents is the essential oils, which are also considered therapeutically active oil, which contain active biologically occurring molecules and, upon topical application, exert a therapeutic effect, which is conceivably synergistic to the beneficial effect of the antibiotic agent in the composition.

[0150] Another class of therapeutically active oils includes liquid hydrophobic plant-derived oils, which are known to possess therapeutic benefits when applied topically.

[0151] Silicone oils (discussed earlier) also may be used and are desirable due to their known skin protective and occlusive properties. Suitable silicone oils include non-volatile silicones, such as polyalkyl siloxanes, polyaryl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers, polydimethylsiloxanes (dimethicones) and poly(dimethylsiloxane)-(diphenyl-siloxane) copolymers. These

are chosen from cyclic or linear polydimethylsiloxanes containing from about 3 to about 9, preferably from about 4 to about 5, silicon atoms. Volatile silicones such as cyclomethicones can also be used. Silicone oils are also considered therapeutically active oil, due to their barrier retaining and protective properties.

[0152] In one or more embodiments, the hydrophobic carrier includes at least 2% by weight silicone oil or at least 5% by weight.

[0153] The solvent may be a mixture of two or more of the above hydrophobic solvents in any proportion.

[0154] A further class of solvents includes "emollients" that have a softening or soothing effect, especially when applied to body areas, such as the skin and mucosal surfaces. Emollients are not necessarily hydrophobic. Examples of suitable emollients include hexyleneglycol, propylene glycol, isostearic acid derivatives, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, sucrose esters of fatty acids, octyl hydroxystearate and mixtures thereof.

[0155] An additional class of emollients, suitable according to the present invention consists of polypropylene glycol (PPG) alkyl ethers, such as PPG stearyl ethers and PPG Butyl Ether, which are polypropylene ethers of stearyl ether that function as skin-conditioning agent in pharmaceutical and cosmetic formulations. PPG alkyl ethers can be incorporated in the foamable composition in a concentration between about 1% and about 20%. The sensory properties of foams containing PPG alkyl ethers are favorable, as revealed by consumer panel tests. Surprisingly, it has been discovered that foams comprising PPG alkyl ethers are non-flammable, as shown in a test according to European Standard prEN

14851, titled "Aerosol containers - Aerosol foam flammability test", while foams containing other oils are inflammable.

[0156] According to one or more embodiments, the hydrophobic organic carrier includes a mixture of a hydrophobic solvent and an emollient. According to one or more embodiments, the foamable composition is a mixture of mineral oil and an emollient in a ratio between 2:8 and 8:2 on a weight basis.

Polar Solvents

[0157] A "polar solvent" is an organic solvent, typically soluble in both water and oil. Examples of polar solvents include polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, such as acetamide oleates such as triolein; various alkanolic acids such as caprylic acid; lactam compounds, such as azone; alkanols, such as dialkylamino acetates, and admixtures thereof.

[0158] According to one or more embodiments, the polar solvent is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof.

[0159] According to one or more embodiments, a moisturizing complex is refers to mixtures of chemical agents specially designed to make the external layers of the skin (epidermis) softer and more pliable, by increasing its hydration

(water content). Naturally occurring skin lipids and sterols as well as artificial or natural oils, humectants, emollients, lubricants, etc. may be used as part of the moisturizing complex. Besides imparting or restoring normal levels of hydration to the skin, the moisturizing complex can have several additional intended and unintended effects on their users, including building a barrier against the loss of water through the epidermis (skin), repairing scaly, damaged or dry skin resulting from external environmental aggressions or internal changes (such as in acne or naturally dry skin), repairing or postponing the aging effects on the skin, etc.

Hydration or Moisturizing Agents

[0160] To combat the potential drying effects of the active agents on the skin, the formulations incorporate a moisturizing complex.

[0161] A moisturizing complex can be prepared from two or more chemical agents, such as stearate, olive oil, water and glycerin. Non-limiting examples of such chemicals may include:

[0162] (a) Humectants, such as glycerin, urea, lactic acid and sorbitol;

[0163] (b) Natural moisturizing factors (NMF) include low molecular weight substances such as ammonia, amino acids, glucosamine, creatinine, citrate and ionic solutions such as sodium, potassium, chloride, phosphate, calcium and magnesium;

[0164] (c) Emollients, such as lanolin (the earliest complex organic substances used in facial and body moisturizers, which is extracted from wool). Lanolin acts as a barrier (occlusion effect) against loss of water and also as a softener of stratum corneum, by means of lubrication and smoothing. Other emollients are oil-water emulsions of varying composition and may include several esters and oils such as octyl dodecanol, hexyl decanol, oleyl alcohol, decyl oleate, isopropyl stearate, isopropyl palmitate, isopropyl myristate, hexyl laureate, and dioctyl cyclohexane; and

[0165] (d) Emulsifier, preserving and fragrance agents are also part of commercial preparations.

[0166] The hydrophobic solvent selected can surprisingly play a significant co moisturizing or hydration effect. For example mineral oil is seen to contribute to the hydration effect in combination with glycerin or with sodium PCA.

[0167] In certain embodiments, the moisturizing complex is a mixture of glycerin and sodium PCA (sodium salt of 2-pyrrolidone-5-carboxylic acid). In certain other embodiments the complex is a mixture of mineral oil glycerin and sodium PCA.

[0168] Derived from the saponification of fats, glycerin (also spelled glycerin and usually referred to in the literature as glycerol) is a strong, nonvolatile trihydroxylated humectant that exhibits hygroscopic ability very similar to that associated with natural moisturizing factor (J. Soc. Cosmet. Chem. 1976;27:65; Acta Derm. Venereol. 1999;79:418-21). Natural moisturizing factor is found in corneocytes and can absorb large quantities of water, even when humidity levels are low, which allows the stratum corneum (SC) to maintain a sufficient hydration level in dry environments. Numerous ingredients have been used in moisturizing products to mimic the activity of natural moisturizing factor, and glycerol is one of the more successful.

Natural Moisturizing Factors

[0169] One of the primary elements in keeping skin healthy is making sure the structure of the epidermis (outer layer of skin) is intact. That structure is defined and created by skin cells that are held together by the intercellular matrix. The intercellular matrix is the "glue" or "mortar" between skin cells that keep them together. It helps prevent individual skin cells from losing water and creates the smooth, non-flaky appearance of healthy, intact skin. The components that do this are often called natural moisturizing factors (NMFs) or ingredients that mimic the structure and function of healthy skin. While the oil and fat components of skin prevent evaporation and provide lubrication to the surface of skin, it is actually the intercellular matrix along with the skin's lipid content that gives skin a good deal of its surface texture and feel.

[0170] The intercellular matrix is the skin's first line of defense against water loss. When the lipid and NMF content of skin is reduced, we experience surface roughness, flaking, fine lines, and a tight, uncomfortable feeling. The longer the skin's surface layer (stratum corneum) is impaired, the less effective the skin's intercellular matrix becomes (Sources: *Skin Research and Technology*, August 2000, pages 128–134; and *Dermatologic Therapy*, Volume 17, Supplement 1, 2004, pages 43-48). Moreover, the skin's healing process is impaired. NMFs make up an expansive group of ingredients that include amino acids, ceramides, hyaluronic acid, cholesterol, fatty acids, triglycerides, phospholipids, glycosphingolipids, urea, linoleic acid, glycosaminoglycans, glycerin, mucopolysaccharide, and sodium PCA (sodium salt of 2-pyrrolidone-5-carboxylic acid). Ingredients that mimic the lipid content of skin are apricot oil, canola oil, coconut oil, corn oil, jojoba oil, jojoba wax, lanolin, lecithin, olive oil, safflower oil, sesame oil, shea butter, soybean oil, squalane, and sweet almond oil, which can all be extremely helpful for making dry skin look and feel better.

[0171] All of the skin's supporting NMFs and lipids are present in the intercellular structure of the epidermis, both between skin cells and in the lipid content on the surface of skin. When any of these ingredients are used in skin-care products, they appear to help stabilize and maintain this complex intercellular-skin matrix. Although none of these very good NMFs and lipids can permanently affect or change skin, they are great at temporarily keeping depleted skin from feeling dry and uncomfortable. More important, all of these ingredients, and many more, can help support the intercellular area of the skin by keeping it intact. This support helps prevent surface irritation from penetrating deeper into the skin, works to keep bacteria out, and aids the skin's immune/healing system. Selecting moisturizers of any kind with NMFs (whether they are labeled as being antiaging, antiwrinkle, serums, lotions, or sunscreens) allows your skin to do its job of repairing and regenerating itself without the impedances brought on when skin is suffering from dryness and excess irritation (Sources: *Clinical Geriatric Medicine*, February 2002, pages 103-120; *Progressive Lipid Research*, January 2003, pages 1-36; *Journal of the European Academy of Dermatology and Venereology*, November 2002, pages 587-594; *Contact Dermatitis*, June 2002,

pages 331-338; *Journal of Investigative Dermatology*, May 1996, pages 1096-1101; *British Journal of Dermatology*, November 1995, pages 679-685; *Skin Pharmacology and Physiology*, September-October 2004, pages 207-213; *Free Radical Research*, April 2002, pages 471-477; and *Journal of Lipid Research*, May 2002, pages 794-804).

[0172] According to one or more embodiments, the moisturizing complex comprises a NMF. In certain embodiments, the NMF is used in combination with one or both of glycerin, sodium pCA. In certain other embodiments the NMF is used in combination with mineral oil and or one or more of glycerin and sodium pCA.

Polymeric Agent

[0173] According to one or more embodiments, the polymeric agent serves to contribute to the viscosity of the formulation, stabilize the foam composition and to control drug residence in the target organ. Exemplary polymeric agents are classified below in a non-limiting manner. In certain cases, a given polymer can belong to more than one of the classes provided below.

[0174] In one or more embodiments, the composition includes at least one gelling agent. A gelling agent controls the residence of a therapeutic composition in the target site of treatment by increasing the viscosity of the composition, thereby limiting the rate of its clearance from the site. Many gelling agents are known in the art to possess mucoadhesive properties. Surprisingly, it has been found that selected and sparing use of such polymeric agents allows the formation of low viscous formulations which nevertheless can hold BPO particles in a suspension that is able to be physically and chemically stable for pharmaceutical use. Moreover the presence of these polymeric agents enables the foam formulation to contribute to controlling the residence of the active agent at the target site.

[0175] The gelling agent can be a natural gelling agent, a synthetic gelling agent and an inorganic gelling agent. Exemplary gelling agents that can be used in accordance with one or more embodiments include, for example, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium

caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, starch, chemically modified starches and the like, semi-synthetic polymeric materials such as cellulose ethers (e.g. hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxy propylmethyl cellulose), guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guar, and the like, and synthetic polymeric materials, such as carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like. Mixtures of the above compounds are contemplated.

[0176] Further exemplary gelling agents include the acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers sold, for example, by the B.F. Goodrich Company under the trademark of Carbopol® resins. In a preferred embodiment the agent is a Carbopol. These resins consist essentially of a colloidal water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with from 0.75% to 2% of a crosslinking agent such as polyallyl sucrose or polyallyl pentaerythritol. Examples include Carbopol® 934, Carbopol® 940, Carbopol® 950, Carbopol® 980, Carbopol® 951 and Carbopol® 981. Carbopol® 934 is a water-soluble polymer of acrylic acid crosslinked with about 1% of a polyallyl ether of sucrose having an average of about 5.8 allyl groups for each sucrose molecule.

[0177] In one or more embodiment, the composition includes at least one polymeric agent, which is a water-soluble cellulose ether. Preferably, the water-soluble cellulose ether is selected from the group consisting of methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (Methocel), hydroxyethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose and carboxymethylhydroxyethylcellulose. More preferably, the water-soluble cellulose ether is selected from the group consisting of methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose (Methocel). In one or more embodiments, the composition includes a combination of a water-soluble cellulose ether; and a naturally occurring polymeric materials, selected from the group

including xanthan gum, guar gum, carrageenan gum, locust bean gum and tragacanth gum.

[0178] Yet, in other embodiments, the gelling agent includes inorganic gelling agents, such as silicone dioxide (fumed silica).

[0179] Mucoadhesive/bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue. Mucoadhesive agents are a class of polymeric biomaterials that exhibit the basic characteristic of a hydrogel, i.e. swell by absorbing water and interacting by means of adhesion with the mucous that covers epithelia. Compositions may contain a mucoadhesive macromolecule or polymer in an amount sufficient to confer bioadhesive properties. The bioadhesive macromolecule enhances the delivery of biologically active agents on or through the target surface. The mucoadhesive macromolecule may be selected from acidic synthetic polymers, preferably having at least one acidic group per four repeating or monomeric subunit moieties, such as poly(acrylic)- and/or poly(methacrylic) acid (e.g., Carbopol®, Carbomer®), poly(methylvinyl ether/maleic anhydride) copolymer, and their mixtures and copolymers; acidic synthetically modified natural polymers, such as carboxymethylcellulose (CMC); neutral synthetically modified natural polymers, such as (hydroxypropyl)methylcellulose; basic amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid, hyaluronic acid, pectin, gum tragacanth, and karaya gum; and neutral synthetic polymers, such as polyvinyl alcohol or their mixtures. An additional group of mucoadhesive polymers includes natural and chemically modified cyclodextrin, especially hydroxypropyl- β -cyclodextrin. Such polymers may be present as free acids, bases, or salts, usually in a final concentration of about 0.01% to about 0.5% by weight.

[0180] A suitable bioadhesive macromolecule is the family of acrylic acid polymers and copolymers, (e.g., Carbopol®). These polymers contain the general structure $-\text{[CH}_2\text{-CH(COOH)-]}_n$. Hyaluronic acid and other biologically-derived polymers may be used.

[0181] Exemplary bioadhesive or mucoadhesive macromolecules have a molecular weight of at least 50 kDa, or at least 300 kDa, or at least 1,000 kDa. Favored polymeric ionizable macromolecules have not less than 2 mole percent acidic groups (e.g., COOH, SO₃H) or basic groups (NH₂, NRH, NR₂), relative to the number of monomeric units. The acidic or basic groups can constitute at least 5 mole percent, or at least 10 mole percent, or at least 25, at least 50 more percent, or even up to 100 mole percent relative to the number of monomeric units of the macromolecule.

[0182] Yet, another group of mucoadhesive agent includes inorganic gelling agents such as silicon dioxide (fumed silica), including but not limited to, AEROSIL 200 (DEGUSSA).

[0183] Many mucoadhesive agents are known in the art to also possess gelling properties.

[0184] The foam composition may contain a film-forming component. The film-forming component may include at least one water-insoluble alkyl cellulose or hydroxyalkyl cellulose. Exemplary alkyl cellulose or hydroxyalkyl cellulose polymers include ethyl cellulose, propyl cellulose, butyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxybutyl cellulose, and ethylhydroxyethyl cellulose, alone or in combination. In addition, a plasticizer or a cross-linking agent may be used to modify the polymer's characteristics. For example, esters such as dibutyl or diethyl phthalate, amides such as diethyldiphenyl urea, vegetable oils, fatty acids and alcohols such as oleic and myristyl acid may be used in combination with the cellulose derivative.

[0185] In one or more embodiments, the composition includes a phase change polymer, which alters the composition behavior from fluid-like prior to administration to solid-like upon contact with the target mucosal surface. Such phase change results from external stimuli, such as changes in temperature or pH and exposure to specific ions (e.g., Ca²⁺). Non-limiting examples of phase change polymers include poly(N-isopropylamide) and Poloxamer 407®.

[0186] The polymeric agent is present in an amount in the range of about 0.01% to about 5.0% by weight of the foam composition. In one or more embodiments, it is typically less than about 1 wt% of the foamable composition. In one or more embodiments, it is formulated to achieve a viscosity in the pre foam formulation of less than about 8000 cps. In certain embodiments the foamable formulation with propellant has a viscosity of less than about 8000 cps and a preferred viscosity in the foamable formulation with propellant of less than about 7000 cps and more preferably less than about 3000 cps. In certain embodiments the ratio of viscosity of the foamable formulation with propellant to the ratio of the viscosity of the pre foam formulation without propellant is between about 1:1, about 19:20; about 9:10; about 4:5; about 3:4; about 3:5; about 2:5 to about 1:5 to about 1:10 preferably between about 19:20 to about 2:5.

[0187] One of the surprising discoveries was that the interaction of the BPO polymeric agent was not destroyed upon addition of high pressure volatile liquid propellant. Without being bound by any theory one possible explanation for the phenomena is that when the emulsion formulation is very viscous and propellant is added the formulation becomes fluid and the change in state from thick to liquid effects the polymeric hold on the BPO, which can then move more and tends to sediment and cake. In contrast when the viscosity was such that the pre-foam formulation was liquid and of low viscosity then adding the high pressurized propellant had only a small or minimal effect on the fluidity of the composition and since the hydrophobic propellant will presumably disperse in the oil phase of the emulsion it will now have relatively minor effect on the formulation, which remains with a similar fluidity and the motion of the BPO is relatively unchanged. Why some polymers are better than others at holding BPO in a fluid homogenous suspension in an emulsion formulation over a prolonged time is not currently understood other than perhaps the ability to have polymer at levels where it would otherwise form a gel but for the use of buffer or pH adjuster to prevent gel formation. In other words the selection of gelling agents which are reversibly susceptible to buffer or pH adjuster addition is an unexpected advantage herein.

Surface Active Agent

[0188] The composition further contains a surface-active agent. Surface-active agents (also termed “surfactants”) include any agent linking oil and water in the composition, in the form of emulsion. A surfactant’s hydrophilic/lipophilic balance (HLB) describes the emulsifier’s affinity toward water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants is usually preferable where the vehicle is an emulsion. In an emulsion environment a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or surfactant combination are not always binding for emulsions and that good quality foams can be produced with a surfactant or surfactant combination both where the HLB values are in or towards the lipophilic side of the scale and where the HLB values are in or towards the hydrophilic side of the scale. Surfactants also play a role in foam formation where the foamable formulation is a single phase composition.

[0189] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9. Lower HLB values may in certain embodiments be more applicable to water in oil emulsions.

[0190] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB values is between about 7 and about 14. Mid range HLB values may in certain embodiments be more suitable for oil in water emulsions.

[0191] According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19. In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

[0192] Preferably, the composition contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embodiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

[0193] In certain embodiments with wax as emollient, surfactants are selected which can provide a close packed surfactant layer separating the oil and water phases. To achieve such objectives combinations of at least two surfactants are selected. Preferably, they should be complex emulgators and more preferably they should both be of a similar molecular type. For example, a pair of ethers like steareth 2 and steareth 21, or a pair of esters for example, PEG-40 stearate and polysorbate 80. In Certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these

combinations due to their versatility and strength may also be used satisfactorily and effectively with wax formulations, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

[0194] It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)] / [DRY-FLO AF Starch], and derivatized dextrin may also a similar stabilizing effect.

[0195] A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 June 2006, Pages 190-193] .

[0196] Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate (Av HLB~11.2); stearate Laureth 4 (HLB~9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

[0197] Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:

Surfactant	HLB
steareth 2	~4.9
glyceryl monostearate/PEG 100 stearate	Av ~11.2
Glyceryl Stearate	~4
Steareth-21	~15.5
peg 40 stearate	~16.9
polysorbate 80	~15
sorbitan stearate	~4.7
laureth 4	~9.7
Sorbitan monooleate (span 80)	~4.3
ceteareth 20	~15.7

steareth 20	~15.3
ceteth 20	~15.7
Macrogol Cetostearyl Ether	~15.7
ceteth 2 (Lipocol C-2)	~5.3
PEG-30 Dipolyhydroxystearate	~5.5
sucrose distearate (Sisterna SP30)	~6
polyoxyethylene (100) stearate	~18.8

[0198] More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

PEG-Fatty Acid Monoester Surfactants

Chemical name	Product example name	HLB
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19

PEG-Fatty Acid Diester Surfactants:

Chemical name	Product example name	HLB
PEG-4 dilaurate	Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4	distearate Kessco .RTM. 200 DS (Stepan.sub)	5
PEG-32 dioleate	Kessco .RTM. PEG 1540 DO (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 disterate	Cithrol 4DS series (Croda)	>10
PEG-20 glyceryl oleate	Tagat .RTM. O (Goldschmidt)	>10

Transesterification Products of Oils and Alcohols

Chemical name	Product example name	HLB
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13

Polyglycerized Fatty Acids, such as:

Chemical name	Product example name	LB
Polyglyceryl-6 dioleate	Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag	8.5

PEG-Sorbitan Fatty Acid Esters

Chemical name	Product example name	HLB
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-20 sorbitan Monopalmitate	Tween 40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15

Polyethylene Glycol Alkyl Ethers

Chemical name	Product example name	HLB
PEG-2 oleyl ether	oleth-2 Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether	oleth-3 Volpo 3 (Croda)	<10
PEG-5 oleyl ether	oleth-5 Volpo 5 (Croda)	<10
PEG-10 oleyl ether	oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether	oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15

PEG-4 lauryl ether	laureth-4Brij 30 (Atlas/ICI)	9.7
PEG-23 lauryl ether	laureth-23Brij 35 (Atlas/ICI)	17
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-2 cetyl ether	Brij 52 (ICI)	5.3

Sugar Ester Surfactants

Chemical name	Product example name	HLB
Sucrose distearate	Sisterna SP50, Surfope 1811	11

Sorbitan Fatty Acid Ester Surfactants

Chemical name	Product example name	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7

[0199] In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable emulsion or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

[0200] Specific non limiting examples of surfactant systems are, combinations of polyoxyethylene alkyl ethers, such as Brij 59 / Brij10; Brij 52 / Brij 10; Steareth 2 / Steareth 20; Steareth 2 / Steareth 21 (Brij 72 / Brij 721);

combinations of polyoxyethylene stearates such as Myrj 52 / Myrj 59; combinations of sucrose esters, such as Surphope 1816 / Surphope 1807; combinations of sorbitan esters, such as Span 20 / Span 80; Span 20 / Span 60; combinations of sucrose esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80 / PEG-40 stearate; methyl glucosyl sequistearate; polymeric emulsifiers, such as Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulse (41) and Montanov (68) and the like.

[0201] In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and cetareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, cetareth 20, ceteth 2 and laureth 4. In certain other embodiments the surfactant is a combination of cetareth 20 and polysorbate 40 stearate. In certain other embodiments the surfactant is a combination of span 60 and GMS. In certain other embodiments the surfactant is a combination of two or all of PEG 40 stearate, sorbitan stearate and polysorbate 60.

[0202] In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

[0203] Without being bound by any particular theory or mode of operation, it is believed that the use of non-ionic surfactants with significant hydrophobic and hydrophilic components, increase the emulsifier or foam stabilization

characteristics of the composition. Similarly, without being bound by any particular theory or mode of operation, using combinations of surfactants with high and low HLB's to provide a relatively close packed surfactant layer may strengthen the emulsion.

[0204] In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

[0205] Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

[0206] In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

[0207] Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect.

[0208] In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

[0209] In one or more embodiments the at least one surface active agent is liquid.

[0210] In one or more embodiments the liquid surfactant is a polysorbate, preferably polysorbate 80 or 60.

[0211] In one or more embodiments the at least one surface active agent is solid, semi solid or waxy.

[0212] It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB values may be of lesser significance in a waterless or substantially non-aqueous environment.

[0213] In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier.

[0214] In one or more embodiments , the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions provided herein.

[0215] Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1

[0216] In one or more embodiments, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about 16:1 and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

[0217] In selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation too viscous or solid. This can be particularly significant if the formulation has high molecular weight, e.g., a high molecular weight PEG or polymeric agents or petroleum or if the surfactants are large. Solvents and polymeric agents which have high molecular weight and are very viscous or solid or waxy (e.g., Peg 1500, 2000, etc. or petrolatum) can exacerbate the effect of a waxy or solid surfactant on shakability or flowability. In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation becomes non shakable and unsuitable. Thus in one embodiment, an effective amount of surfactant may be used provided the formulation remains shakable. In other certain exceptional embodiments the upper limit may be determined by flowability such as in circumstances where

the composition is marginally or apparently non-shakable. The formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam.

[0218] In certain embodiments the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15%. or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiment the concentration of surface active agent is between about 1% and about 6%.

[0219] In one or more embodiments the surfactant comprises a polymeric surfactant.

[0220] In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE – free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

[0221] If the composition as formulated is a substantially non shakable composition it is nevertheless possible as an exception in the scope for the formulation to be flowable to a sufficient degree to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This surprising and unusual exception may be due one or more of a number of factors such as the high viscosity, the softness, the lack of crystals, the

pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

[0222] In one or more embodiments, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher phase inversion and tension.

[0223] Phase inversion is a factor in the preparation and stabilization of emulsions and can be both an aid and a detriment. Phase inversion involves the change of emulsion type from o/w to w/o or vice versa. Prior to phase inversion occurring there is a tension in the emulsion which if destabilized or driven will lead to phase inversion and if controlled or ameliorated or dissipated will result in a more stable emulsion. The occurrence of phase inversion during preparation can be a sign of instability. If controlled, it can result in a finer product but if due to other factors after the emulsion was prepared it can cause problems. Inversion can occur by for example adding calcium chloride to an o/w emulsion stabilized with sodium stearate to form calcium stearate. Inversion can also occur as the product of changes to the phase- volume ratio. For example if a small amount of water is added to surfactant mixed with oil and agitated a w/o emulsion is formed. As the amount of water added is gradually increased a point will be reached where the water and emulsifier envelop the oil as small droplets to form an o/w emulsion. The amount of each ingredient including the surfactants will have their part to play in the phenomenon.

Substantially Alcohol-Free

[0224] According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and includes less than about 5% final concentration

of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Substantially Non Aqueous

[0225] In certain cases, the active agent degrades in the presence of water, and therefore, in such cases the presence of water in the composition is not desirable. Thus, in certain preferred embodiments, the composition is substantially non-aqueous. The term “substantially non-aqueous” or “substantially waterless” is intended to indicate that the composition has a water content below about 25%.

Shakability

[0226] ‘Shakability’ means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases possibly aided by the presence of silicone it may exceptionally be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

[0227] A breakable foam is one that is thermally stable, yet breaks under shear force.

[0228] The breakable foam herein is not “quick breaking” and is not “thermolabile”, i.e., it does not collapse quickly upon expulsion and it does not readily collapse or melt upon exposure to body temperature environment. The breakable foam further does not display a long delayed expansion over minutes. Stability over a short time frame of minutes has advantages over foam which collapses quickly upon release. Similarly shear-force breakability of the foam is clearly advantageous over thermally induced breakability. Both these factors allow for comfortable application and well directed administration to the target area. Breakable foam can break readily upon the application of shear force such as gentle rubbing to spread easily over a target surface. The shear-force breakable foams herein are of low density, which further assists spreadability and contributes to a light pleasant feel.

Foam Adjuvant

[0229] Preferably, a therapeutically effective foam adjuvant is included in the foamable compositions herein to increase the foaming capacity of surfactants and/or to stabilize the foam. In one or more embodiments, the foam adjuvant agent includes fatty alcohols having 15 or more carbons in their carbon chain, such as cetyl alcohol and stearyl alcohol (or mixtures thereof). Other examples of fatty alcohols are arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are especially well suited as foam adjuvant agents. The amount of the fatty alcohol required to support the foam system is inversely related to the length of its carbon chains. Foam adjuvants, as defined herein are also useful in facilitating improved spreadability and absorption of the composition.

[0230] In one or more embodiments, the foam adjuvant agent includes fatty acids having 16 or more carbons in their carbon chain, such as hexadecanoic acid (C16) stearic acid (C18), arachidic acid (C20), behenic acid (C22), octacosanoic acid (C28), as well as fatty acids with longer carbon chains (up to C50), or mixtures thereof. As for fatty alcohols, the amount of fatty acids required to support the foam system is inversely related to the length of its carbon chain.

[0231] In one or more embodiments, a combination of a fatty acid and a fatty ester is employed.

[0232] Optionally, the carbon atom chain of the fatty alcohol or the fatty acid may have at least one double bond. A further class of foam adjuvant agent includes a branched fatty alcohol or fatty acid. The carbon chain of the fatty acid or fatty alcohol also can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

[0233] An important property of the fatty alcohols and fatty acids used in context of the compositions herein is related to their therapeutic properties per se. Long chain saturated and mono unsaturated fatty alcohols, e.g., stearyl alcohol,

erucyl alcohol, arachidyl alcohol and behenyl alcohol (docosanol) have been reported to possess antiviral, antiinfective, antiproliferative and anti-inflammatory properties (see, U.S. Patent No. 4,874,794). Longer chain fatty alcohols, e.g., tetracosanol, hexacosanol, heptacosanol, octacosanol, triacontanol, etc., are also known for their metabolism modifying properties and tissue energizing properties. Long chain fatty acids have also been reported to possess anti-infective characteristics.

[0234] Thus, in preferred embodiments, a combined and enhanced therapeutic effect is attained by including BPO, an antibiotic agent and a therapeutically effective foam adjuvant in the same composition, thus providing a simultaneous anti-inflammatory and antiinfective effect from both components. Furthermore, in a further preferred embodiment, the composition concurrently comprises an antibiotic agent, a therapeutically effective foam adjuvant and a therapeutically active oil, as detailed above. Such combination provides an even more enhanced therapeutic benefit. Thus, the foamable carrier, containing the foam adjuvant provides an extra therapeutic benefit in comparison with currently used vehicles, which are inert and non-active.

[0235] The foam adjuvant according to one or more preferred embodiments includes a mixture of fatty alcohols, fatty acids and hydroxy fatty acids and derivatives thereof in any proportion, providing that the total amount is 0.1% to 5% (w/w) of the carrier mass. More preferably, the total amount is 0.4% - 2.5% (w/w) of the carrier mass.

[0236] Optionally, the composition further contains a penetration enhancer. Non limiting examples of penetration enhancers include propylene glycol, butylene glycols, glycerol, pentaerythritol, sorbitol, mannitol, oligosaccharides, dimethyl isosorbide, monooleate of ethoxylated glycerides having about 8 to 10 ethylene oxide units, polyethylene glycol 200-600, transcutool, glycofurol and cyclodextrins.

[0237] The therapeutic foam may further optionally include a variety of formulation excipients, which are added in order to fine-tune the consistency of the formulation, protect the formulation components from degradation and oxidation and modify their consistency. Such excipients may be selected, for

example, from stabilizing agents, antioxidants, humectants, preservatives, colorant and odorant agents and other formulation components, used in the art of formulation.

Propellants

[0238] Aerosol propellants are used to generate and administer the foamable composition as a foam. Suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

[0239] In an embodiment the propellant is AP 70 which is a mixture of propane, isobutene and butane. In another embodiment the propellant is AP 46 which is a similar mixture of propane, isobutene and butane but having a lower pressure. AP 70 offers about 50% higher pressure than AP 46.

[0240] The propellant makes up about 3-25 wt% of the foamable composition. In some circumstances the propellant may be up to 35%. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients can be referred to as the foamable composition.

[0241] Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers - Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

[0242] Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect include propellants made by DuPont under the registered

trademark Dymel, such as 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227). HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

[0243] Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

[0244] In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butane or mixtures of hydrocarbon propellants such as propane, isobutane and butane.

AGING

[0245] In order to project the potential shelf life and stability of the compositions and their ingredients particularly active or benefit agents the compositions can be subjected to a number of tests, including centrifugation to look for resistance to creaming, phase separation; one or more freeze thaw cycles, standing at room and higher temperatures as an indicator of resistance to aging.

Composition and Foam Physical Characteristics

[0246] A pharmaceutical or cosmetic composition manufactured using the foam carrier according to one or more embodiments is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0247] The foam composition creates a stable formulation having an acceptable shelf-life of at least six months, preferably at least one year, or more preferably at least two years at ambient temperature. A feature of a product for cosmetic or medical use is long term stability. Propellants, which are usually a mixture of low molecular weight hydrocarbons, tend to impair the stability of emulsions and can cause accelerated breakdown of the active ingredient. It has been observed, however, that foam compositions according to the present

invention are surprisingly stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

[0248] The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

[0249] Foam quality can be graded as follows:

[0250] Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

[0251] Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

[0252] Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

[0253] Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

[0254] Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

[0255] Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

[0256] Typically administratable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge

from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

[0257] A further aspect of the foam is breakability. The breakable foam is thermally stable, yet breaks easily under sheer force. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and begin to be absorbed, and therefore, cannot be applied on the hand and afterwards delivered to the afflicted area a minute or so later since the foam will have practically disappeared.

[0258] Another property of the foam is density (specific gravity), as measured upon release from the aerosol can. Typically, foams have low specific gravity of (1) less than 0.12 g/mL; or (2) the range between 0.02 and 0.12; or (3) the range between 0.04 and 0.10; or (4) the range between 0.06 and 0.10.

[0259] A further factor is Bubble size. Typically, quality foams have a low bubble size with the average bubble size being below about 300 microns, preferably being below about 200 microns more preferably being below about 120 microns.

METHODS

Production under vacuum

[0260] Optionally, the foamable formulation may be produced under nitrogen and under vacuum. Whilst the whole process can be carried out under an oxygen free environment, it can be sufficient to apply a vacuum after heating and mixing all the ingredients to obtain an emulsion or homogenous liquid. Preferably the production chamber is equipped to apply a vacuum but if not the formulation can be for example placed in a dessicator to remove oxygen prior to filling and crimping.

Canisters Filling and Crimping

[0261] Each aerosol canister is filled with the pre-foam formulation ("PFF") and crimped with valve using vacuum crimping machine. The process of applying a

vacuum will cause most of the oxygen present to be eliminated. Addition of hydrocarbon propellant may without being bound by any theory further help to reduce the likelihood of any remaining oxygen reacting with the active ingredient. It may do so, without being bound by any theory, by one or more of dissolving in the oil or hydrophobic phase of the formulation, by dissolving to a very limited extent in the aqueous phase, by competing with some oxygen from the formulation, by diluting out any oxygen, by a tendency of oxygen to occupy the dead space, and by oxygen occupying part of the space created by the vacuum being the unfilled volume of the canister or that remaining oxygen is rendered substantially ineffective in the formulation.

Pressurizing

Propellant Filling

[0262] Pressurizing is carried out using a hydrocarbon gas or gas mixture. Canisters are filled and then warmed for 30 sec in a warm bath at 50°C and well shaken immediately thereafter.

Closure Integrity Test.

[0263] Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60°C water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

TESTS

[0264] By way of non limiting example the objectives of hardness, collapse time, viscosity, bubble size and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

Hardness

[0265] LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can effect the degree of dermal

penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

Collapse Time

[0266] Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.

Viscosity

[0267] Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1RPM may be measured, although the figures are of a higher magnitude. Unless otherwise stated viscosity of the pre-foam formulation (PFF) is provided. It is not practical to try and measure the viscosity of the foamable formulation with regular propellants since they have to be stored in sealed pressurized canisters or bottles. In order to simulate the viscosity in the foamable formulations with propellant an equivalent weight of pentane (a low volatile hydrocarbon) is added to and mixed with the pre-foam formulation and left overnight. The viscosity is then measured as above.

FTC (Freeze Thaw Cycles)

[0268] To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc., commencing with -10°C (24hours) followed by +40°C (24hours) measuring the appearance and again repeating the cycle for up to four times.

Density

[0269] In this procedure, the foam product is dispensed into vessels (including dishes or tubes) of a known volume and weight. Replicate measurements of the mass of foam filling the vessels are made and the density is calculated. The canister and contents are allowed to reach room temperature. Shake the canister

to mix the contents and dispense and discard 5-10 mL. Then dispense foam into a preweighed tube, filling it until excess is extruded. Immediately remove (level off) excess foam at both ends and weigh the filled tube on the weighing balance.

Creaming by centrifugation

Principle of test

[0270] The centrifugation used in this procedure serves as a stress condition simulating the aging of the liquid dispersion under investigation. Under these conditions, the centrifugal force applied facilitates the coalescence of dispersed globules or sedimentation of dispersed solids, resulting in loss of the desired properties of the formulated dispersion.

Procedure

[0271] Following preparation of the experimental formulation/s, allow to stand at room temperature for ≥ 24 h. Handle pentane in the chemical hood. Add to each experimental formulation in a 20-mL glass vial a quantity of pentane equivalent to the specified quantity of propellant for that formulation, mix and allow formulation to stand for at least 1 h and not more than 24 h.

[0272] Transfer each mixture to 1.5 mL microtubes. Tap each microtube on the table surface to remove entrapped air bubbles.

[0273] Place visually balanced microtubes in the centrifuge rotor and operate the centrifuge at one or more of 10,000 rpm for 10 min, 3,000 rpm for 10 min or at 1,000 rpm for 10 min.

Visual Stability Tests

Spillability

[0274] An objective in designing formulations it to formulate so the composition does not lose fluidity, and stays spillable after the incorporation of active agent. Spillability means free moving or rotating of formulation inside the glass bottle upon inversion.

Bubble Size

[0275] Foams are made of gas bubbles entrapped in liquid. The bubble size and distribution reflects in the visual texture and smoothness of the foam. Foam bubbles size is determined by dispensing a foam sample on a glass slide, taking a picture of the foam surface with a digital camera equipped with a macro lens. The diameter of about 30 bubbles is measured manually relatively to calibration standard template. Statistical parameters such as mean bubble diameter, standard deviation and quartiles are then determined. Measuring diameter may also be undertaken with image analysis software. The camera used was a Nikon D40X Camera (resolution 10MP) equipped with Sigma Macro Lens (ref: APO MACRO 150mm F2.8 EX DG HSM). Pictures obtained are cropped to keep a squared region of 400 pixels x 400 pixels.

Microscope size:

[0276] The light microscope enables observing and measuring particles from few millimeters down to one micron. Light microscope is limited by the visible light wavelength and therefore is useful to measuring size of particles above 800 nanometers and practically from 1 micron (1,000 nanometers).

Shakability

[0277] Shakability represents the degree to which the user is able to feel / hear the presence of the liquid contents when the filled pressurized canister is shaken. Shaking is with normal mild force without vigorous shaking or excessive force. When the user cannot sense the motion of the contents during shaking the product may be considered to be non shakable. This property may be of particular importance in cases where shaking is required for affecting proper dispersion of the contents.

Shakability scoring :

Shakability	
Good shakability (conforms to required quality specification)	2
Moderate shakability (conforms to required quality specification)	1
Not shakable (fails to meet required quality specification) but may still be flowable and allow foam formation of quality	0
Is substantially not able to pass through valve	Block

BPO ANALYTICAL METHOD (used in section C)

UPLC determination of benzoyl peroxide and degradation products in pressurized formulation and pre foam formulation

[0278] An ultra performance liquid chromatography (UPLC) method was used for determining the concentration of the active ingredient BPO and the main degradation product, benzoic acid, and the presence of other degradation products in benzoyl peroxide pre-foam formulations (PFF) and pressurized formulations (PF).

[0279] About 270 mg of foam or pre-foam formulation is dissolved in acetonitrile (ACN), sonicated in cold water, mixed and filtered. The filtrate is analyzed by UPLC using a C-18 column; elution is performed with a mobile phase containing water: ACN : Methanol: Acetic acid, 45:45:10:0.1 (v/v/v/v). The peak area is determined.

[0280] The content of benzoyl peroxide, benzoic acid and other impurities in the tested sample is calculated from the ratio between the respective peak area of the samples and the average peak area of an ethyl benzoate (EB) standard (0.32mg/mL) with respect to a response factor (based on the absorbance ratio

between EB and BPO). Ethyl Benzoate was found to be a more reliable standard for BPO since discrepancies are observed in the potency of BPO standards on prolonged testing probably due to inter alia the variability of moisture in the BPO standard.

Fields of Pharmaceutical Applications

[0281] According to one aspect, a method of treating acne is provided, the method comprising administering topically to a subject having acne a foamed composition as described herein. According to another aspect a method of treating other disorders responsive to BPO is provided. According to further aspects a method of treating acne and/or other disorders responsive to BPO and antibiotics is provided. According to still further aspects a method of treating acne and/or other disorders responsive to BPO and other drugs is provided.

[0282] According to another aspect, there is provided a method of enhancing the stability of a foamable composition comprising benzoyl peroxide for treating acne, the method comprising adding a moisturizing complex to the foamable composition. In certain embodiments of this aspect, the moisturizing complex comprises about 5% to about 15% by weight of the total composition not including any oils, which may contribute to improved hydration. In certain other embodiments of this aspect, the moisturizing complex comprises glycerin and sodium PCA. In further aspects the moisturizing complex comprises mineral oil together with one or both of glycerin and sodium PCA. Applicants have surprisingly found that the stability of foamable compositions containing benzoyl peroxide can be enhanced by adding glycerin/pCA to the compositions. Without being bound by any theory the presence of mineral oil or other occlusive oils may also help to prevent water loss and encourage rehydration.

[0283] According to a further aspect, there is provided a method of reducing the dryness and/or irritation associated with the use of a composition containing benzoyl peroxide in treating acne, the method comprising adding a moisturizing complex to the composition. In certain embodiments of this aspect, the moisturizing complex comprises about 5% to about 15% by weight of the total composition not including any oils, which may contribute to improved hydration..

In certain other embodiments of this aspect, the moisturizing complex comprises glycerin and sodium PCA. In further aspects the moisturizing complex comprises mineral oil together with one or both of glycerin and sodium PCA.

[0284] The foamable composition herein is suitable for administration to an afflicted area, in need of treatment, including, but not limited to the skin, a body surface, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum (severally and interchangeably termed herein "target site").

[0285] Not only are the foamable carrier formulations described herein suitable for delivering BPO on its own or in combination with a one or more compatible active agents that do not help or cause break down of BPO but active agents may be used in and delivered by the said foamable carrier formulations without BPO. In other words whilst the specification describes carriers suitable for BPO, these novel carriers having been discovered and developed can also be used to carry other API's and cosmetic agents described herein. In a particular aspect such foamable carriers can be used to provide homogenous suspensions of insoluble active agents. Non-limiting examples of other solid active agents include Imiquimod (for example, at about 1-5%) and similar compounds; Acyclovir (for example, at about 5%) and similar compounds such as Cyclovir, Acivir, and Zovir; corticosteroids (for example, at about 0.5% or more); encapsulated drugs, wherein the encapsulation or entrapping agent is insoluble, such as Microsponge, silica and other such species; particles, such as polymer microspheres (for example, polyheal); zinc oxide, titanium oxide, silicone oxide (silica) and other insoluble inorganic therapeutic agents

[0286] Antibiotic agents are initially thought to affect disorders that involve blood circulation abnormalities, yet, in many case, circulation lays a secondary, yet influential role, which must be taken into account in order to optimize treatment. For example, cutaneous malignant tumors are characterized by poor blood circulation, which make them less responsive to drug treatment, and therefore usage of an antibiotic agent would be beneficial to the cancer therapy.

[0287] Thus, by including an appropriate antibiotic agent and optionally, additional active agents in the composition, the kit and the composition herein are useful in treating an animal or a patient having one of a variety of dermatological disorders (also termed "dermatoses") and/or having any secondary condition resulting from infections, which disorders and/or conditions are classified in a non-limiting exemplary manner according to the following groups:

[0288] Any disorders that involve a microbiological infection, or disorders that respond to treatment with an antibiotic agent,

[0289] An infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

[0290] Any one of a variety of dermatological disorders, including dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, grannuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns,

scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo.

[0291] Dermatitis including contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular dermatitis, chronic dermatitis of the hands and feet, generalized exfoliative dermatitis, stasis dermatitis; lichen simplex chronicus; diaper rash;

Bacterial infections including cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, staphylococcal scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, erythrasma;

Fungal Infections including dermatophyte infections, yeast Infections; parasitic Infections including scabies, pediculosis, creeping eruption;

Viral Infections, including, but not limited to herpes genitalis and herpes labialis;

Disorders of hair follicles and sebaceous glands including acne, rosacea, perioral dermatitis, hypertrichosis (hirsutism), alopecia, including male pattern baldness, alopecia areata, alopecia universalis and alopecia totalis; pseudofolliculitis barbae, keratinous cyst;

Scaling papular diseases including psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris;

Benign tumors including moles, dysplastic nevi, skin tags, lipomas, angiomas, pyogenic granuloma, seborrheic keratoses, dermatofibroma, keratoacanthoma, keloid;

Malignant tumors including basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease of the nipples, Kaposi's sarcoma;

Reactions to sunlight including sunburn, chronic effects of sunlight, photosensitivity;

Bullous diseases including pemphigus, bullous pemphigoid, dermatitis herpetiformis, linear immunoglobulin A disease;

Pigmentation disorders including hypopigmentation such as vitiligo, albinism and postinflammatory hypopigmentation and hyperpigmentation such as melasma (chloasma), drug-induced hyperpigmentation, postinflammatory hyperpigmentation;

Disorders of cornification including ichthyosis, keratosis pilaris, calluses and corns, actinic keratosis;

Pressure sores;

Disorders of sweating; and

Inflammatory reactions including drug eruptions, toxic epidermal necrolysis; erythema multiforme, erythema nodosum, granuloma annulare.

[0292] According to one or more embodiments, the compositions are also useful in the therapy of non-dermatological disorders by providing transdermal delivery of an active antibiotic agent that is effective against non-dermatological disorders.

[0293] The same advantage is expected when the composition is topically applied to a body cavity or mucosal surface (e.g., the mucosa of the nose and mouth, the eye, the ear canal, vagina or rectum) to treat conditions such as chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum.

[0294] In an embodiment, the composition is useful for the treatment of one or more of skin irritations, wound, ulcer and burn. This use is particularly important

since the composition preads easily on the afflicted area, without the need of extensive rubbing. Similarly it can be used for prophylactic purposes and as a disinfectant.

[0295] In light of the expansion of the foam upon administration, it is further suitable for the treatment and prevention of post-surgical adhesions. Adhesions are scars that form abnormal connections between tissue surfaces. Post-surgical adhesion formation is a natural consequence of surgery, resulting when tissue repairs itself following incision, cauterization, suturing, or other means of trauma. When comprising an antibiotic agent and optionally, appropriate protective agents, the foam is suitable for the treatment or prevention of post surgical adhesions.

[0296] Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on October 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on September 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0018937, published on January 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on December 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on November 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on January 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on August 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. Publication No. 2007-0292355 published on December 20, 2007 and entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Publication No. 2008-0069779 and entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Publication 20080206159, published on August 28, 2008 and entitled COMPOSITIONS WITH MODULATING AGENTS; U.S. Patent Application No. 11/767,442, filed on June 22, 2007, entitled FOAMABLE COMPOSITIONS AND KITS COMPRISING ONE

OR MORE OF A CHANNEL AGENT, A CHOLINERGIC AGENT, A NITRIC OXIDE DONOR, AND RELATED AGENTS AND THEIR USES; U.S. Publication 2008-0069779, published on March 20, 2008 and entitled FOAMABLE VEHICLE AND VITAMIN AND FLAVONOID PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entireties with reference to any of the active ingredients; penetration enhancers; humectants; moisturizers; listed therein can be applied herein and are incorporated by reference.

[0297] The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full-intended scope of the appended claims.

[0298] Table of Ingredients Used

Ingredients	Brand name	Category	HLB	RHLB
Polysorbate 60	Tween 60	Surfactant	14.9	
Polysorbate 20	Tween 20	Surfactant	16.7	
Polysorbate 80	Tween 80	Surfactant	15	
Ceteth 20	Lipocol C-20	Surfactant	15.4	
Steareth 2	Brij 72	Surfactant	4.9	
sreareth 21	Brij 721	Surfactant	15.5	
PEG 40-stearate	Myrj 52	Surfactant	16.9	
PEG 100-stearate	Myrj 59	Surfactant	18.8	
sorbitan laurate	Span 20	Surfactant	8.6	
sorbitan stearate	Span 60	Surfactant	4.7	
sorbitan palmitate	Span 40	Surfactant	6.7	
Glyceryl monostearate	Cutina GMS	Surfactant	3.8	
Stearyl alcohol	Speziol C-18	Foam adjuvant		15.5
Cetostearyl alcohol	Speziol C 16-18	Foam adjuvant		15.5
Cocoglycerides	Novata A	Thickener		~8
Sodium Carboxymethyl cellulose (30000)	Cekol 30000	Polymer		
Hydroxypropyl methylcellulose	Methocel K100M	Polymer		
Xanthan gum	Xantural 11K	Polymer		
hydroxypropyl cellulose	Klucel EF	Polymer		
Aluminum starch octenylsuccinate	DryFlo plus	Polymer		
Carbomer 941	Carbopol 981	Polymer		

Ingredients	Brand name	Category	HLB	RHLB
Carbomer 940	Carbopol 980	Polymer		
Carbomer 934P	Carbopol 974P	Polymer		
Crospovidone CL-M	Poly (Vinylpolypyrrolidone)	Polymer		
Cyclopentasiloxane	Cyclomethicone	Emollient		7.75
Joboba Oil	Jojoba Oil	Emollient		6.5
light Mineral oil	pioneer 2076p	Emollient		10.5
Caprylic/Caprylic triglycerides	MCT oil	Emollient		5
Citric acid	Citric acid	buffer agent		
Sodium Citrate	Sodium Citrate	buffer agent		
Sodium hydroxide	Sodium hydroxide	pH agent		
Triethanolamine	Triethanolamine	pH agent		
Purified water	Purified water	Solvent		
Propylene glycol	Propylene glycol	Humectant		
Glycerin	Glycerin	Humectant		
sodium salt of pyrrolidone carbonic acid	Sodium PCA	Humectant		
Benzoyl Peroxide	Benzoyl Peroxide	API		
propane+butane+isobutene (AP-70)		Propellant		

[0299] As BPO can be an irritant the ingredients used in the formulations were identified as being non irritants in the concentrations used.

EXAMPLES

The Examples below describe the experimental development of the BPO formulations provided herein.

SECTION A – Non Oil Aqueous Formulations with BPO

[0300] The examples below have between about in excess of 70% to about in excess of 90% water and no oil save some examples contain either an emollient foam adjuvant or an emulsifying mix.

Example 1- Over about 90% water and 1% CMC as polymer

	009	010	011	013	017
chemical name					
Polysorbate 60	1.00		1.00		
Stearyl alcohol			1.00	1.00	2.00
Sodium Carboxymethyl cellulose (30000)	1.00	1.00	1.00	1.00	1.00
Purified water	92.0	93.0	91.0	92.0	91.0
Benzoyl Peroxide	6.0	6.0	6.0	6.0	6.0
Control:	100.00	100.00	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00	8.00	8.00
Results					
QUALITY	G-E	P	G-E	FG	FG
COLOR	W		W	W	W
ODOR	NO ODOR		NO ODOR	NO ODOR	NO ODOR
SHAKABILITY	GOOD		GOOD	GOOD	GOOD
visual inspection (presurized glass bottle)	non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility		non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility		
Collapse time (sec.)	110/F		90/FG		

G-E=Good to Excellent; FG= Fairly Good; and P= Poor; No reversibility-= Upon shaking large BPO large particals were still observed during shaking, which immediately sedimented when shaking ended.

[0301] Comments: In this case, a surfactant (e.g. Polysorbate 60) is required to obtain good foam. In the presence of BPO, CMC polymer without surfactant resulted in poor foam. Addition of foam adjuvant improved matters and produced fairly good foam. However, doubling the amount of the foam adjuvant did not result in any further significant improvement. CMC polymer with surfactant did

result in good quality foam but addition of foam adjuvant did not in this case appear to help. Collapse time is moderate and homogeneity requires attention.

Manufacturing procedure (009)

Step 1: Preparation of Water Phase (A)

- 1.1. Heat water to 60-65°C, add CMC while stirring
- 1.2. add Polysorbate 60 while mixing
- 1.3. cool to RT

Step 2: Benzoyl peroxide addition

Add Benzoyl peroxide. Mix thoroughly

Step 3: Homogenization

Homogenize 15 minutes.

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (010)

Step 1: Preparation of Water Phase (A)

- 1.1. Heat water to 60-65°C, add CMC while stirring
- 1.2. cool to RT

Step 2: Benzoyl peroxide addition

Add Benzoyl peroxide. Mix thoroughly

Step 3: Homogenization

Homogenize 15 minutes

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (011)

Step 1: Preparation of Water Phase (A)

- 1.1. Heat water to 60-65°C, add CMC stirring.

1.2. add Polysorbate 60 and Stearyl alcohol

1.3. cool to RT

Step 2: Benzoyl peroxide addition

Add Benzoyl peroxide. Mix thoroughly.

Step 3: Homogenization

Homogenize 15 minutes.

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (013)

Step 1: Preparation of Water Phase (A)

1.1. Heat water to 60-65°C, add CMC while stirring.

1.2. add Stearyl alcohol

1.3. cool to RT

Step 2: Benzoyl peroxide addition

Add Benzoyl peroxide. Mix thoroughly.

Step 3: Homogenization

Homogenize 15 minutes

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (017)

Step 1: Preparation of Water Phase (A)

1.1. Heat water to 60-65°C, add CMC while stirring

1.2. add Stearyl alcohol

1.3. Cool to RT

Step 2: Benzoyl peroxide addition

Add Benzoyl peroxide. Mix thoroughly.

Step 3: Homogenization

Homogenize 15 minutes.

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Example 2- Over about 90% water and 0.7% Xanthan/Methocel as Polymer

	012	015	014	016
chemical name				
Polysorbate 60	1.00		1.00	
Stearyl alcohol			1.00	1.00
Hydroxypropyl methylcellulose (Methocel K100M)	0.35	0.35	0.35	0.35
Xanthan gum	0.35	0.35	0.35	0.35
Purified water	92.3	93.3	91.3	92.3
Benzoyl Peroxide	6.0	6.0	6.0	6.0
Control:	100.00	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00	8.00
Results				
QUALITY	G-E	G-E	G-E	F
COLOR	W	W	W	
ODOR	NO ODOR	NO ODOR	NO ODOR	
SHAKABILITY	GOOD	GOOD	GOOD	
visual inspection (presurized glass bottle)	non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility	non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility	non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility	non homog.-white,opaque amorphous particals dispensed in liquid,no reversibility
Collapse time (sec.)	100/F	>300/E	180/FG	

No reversibility== Upon shaking large BPO large particals were still observed during shaking, which immediately sedimented when shaking ended

[0302] Comments: Replacing CMC polymer with xanthan / methocel as polymer results in good to excellent foam even without surfactant that has a collapse time in excess of 5 minutes. Methocel is a gelling polymer that in addition to being a gelling agent can have a stabilizing effect of suspensions and emulsions. Surprisingly the addition of surfactant reduces the collapse time and although the addition of foam adjuvant improves the collapse time the polymeric combination alone surprisingly results in the better formulation. Also surprising is that addition of Foam Adjuvant to the xanthan / methocel polymer formulation without surfactant results in only Fair foam, where as without the adjuvant results in good to excellent foam. This may be due to there being not enough stabilizing power from the polymeric agents to stabilize the fatty acid in the water medium. Homogeneity requires attention.

Manufacturing procedure (012)

Step 1: Preparation of Water Phase (B)

- 1.1.Heat part of water to 90°C, Add Methocel K100M with agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.
- 1.2.Heat (Step 1.1) to 50°C, add Xanthan gum with vigorous mixing. Add Polysorbate 60 .
- 1.3.cool to RT

Step 2: Homogenization

- 2.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.
- 2.2. add water if necessary to obtain the correct weight.

Step 3: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 4: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (014)**Step 1: Preparation of Water Phase (B)**

1.1. Heat part of water to 90°C, Add Methocel K100M with agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.

1.2 Heat (Step 1.1) to 50°C, add Xanthan gum with vigorous mixing. Add Polysorbate 60.

1.3 cool to RT

Step 2: Homogenization

Add Benzoyl peroxide and homogenize for 15 minutes at 8000 RPMs while cooling with ice bath.

Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 3: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 4: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (015)**Step 1: Preparation of Water Phase (B)**

1.1. Heat part of water to 90°C, Add Methocel K100M with agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.

1.2 Heat (Step 1.1) to 50°C, add Xanthan gum with vigorous mixing. Add Polysorbate 60 and Stearyl alcohol.

1.3 cool to RT

Step 2: Homogenization

Add Benzoyl peroxide and homogenize for 15 minutes at 8000 RPMs while cooling with ice bath.

Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 3: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 4: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (016)

Step 1: Preparation of Water Phase (B)

1.2. Heat part of water to 90°C, Add Methocel K100M with agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.

1.2 Heat (Step 1.1) to 50°C, add Xanthan gum with vigorous mixing. Add Stearyl alcohol.

1.3 cool to RT

Step 2: Homogenization

Add Benzoyl peroxide and homogenize for 15 minutes at 8000 RPMs while cooling with ice bath.

Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 3: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 4: Pressurizing

Canisters are filled with 8% propellant.

Example 3- Over about 80% water and high amounts polymer (about 7% to about % of Klucel or CMS with or without ASOS)

	019	020	022
chemical name			
Polysorbate 60	2.00	2.00	2.00
Sodium Carboxymethyl cellulose (30000)		7.00	
Klucel EF	7.00		7.00
ASOS			2.00
Benzoyl Peroxide	6.0	6.0	6.0
Purified water	85.0	85.0	83.0
Control:	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00
Results			
Viscosity (PFF)	307.93		184.96
QUALITY	G-E	BLOCK	G-E
COLOR	W		W
ODOR	NO ODOR		NO ODOR
SHAKABILITY	GOOD		GOOD
Density	0.035		0.035
Collapse time (sec.)			>300/FG
FTC			
foam quality			E
color			White
odor			very faint odor
shakability			good

[0303] Comments: High levels of CMC resulted in the formulation blocking the valve. However, when Klucel was used at high levels (7%) with and without ASOS (Aluminum Starch Octenylsuccinate) good to excellent foam was obtained.

Manufacturing procedure (019)**Step 1: Preparation of Water Phase**

- a. Add Klucel EF to water at 40C while vigorously stirring.
- b. Heat to 40-50C and add polysorbate 60 while stirring.
- c. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- d. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (020)**Step 1: Preparation of Water Phase**

- a. Add NaCMC to water at 40C while vigorously stirring.
- b. Heat to 40-50C and add polysorbate 60 while stirring.
- c. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- d. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (022)**Step 1: Preparation of Water Phase**

- a. Add Klucel EF and ASOS to water at 40C while vigorously stirring.
- b. Heat to 40-50C and add polysorbate 60 while stirring.
- c. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- d. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Example 4 - Over about 80% water plus surfactants without polymeric agents

	021	032
chemical name		
Polysorbate 20	3.00	3.00
Ceteth 20	2.00	3.00
sreareth 21		2.00
PEG 100-stearate	3.00	2.00
Purified water	85.0	84.0
Benzoyl Peroxide	6.0	6.0
Control:	100.00	100.00
Propellant (AP-70)	8.00	8.00
Results		
Viscosity (PFF)		5
QUALITY	G-E	G-E
COLOR	W	W
ODOR	NO ODOR	NO ODOR
SHAKABILITY	GOOD	GOOD
Density		0.041
Bubble size (µm)		107
Bubble size (above 500µm)		0.0
Collapse time (sec.)		>300/G

[0304] Comments: The combination surfactant systems used were able to generate good to excellent foams. Combinations or complex emulgators are generally superior in emulsion stability and foam quality. Also, combinations or complex emulgators contribute to collapse time especially when surfactants are solid at room temp.

Manufacturing procedure (021, 032)

- a. Add all ingredients to water at 50C while vigorously stirring till complete dissolution.
- b. Cool to RT and Add Benzoyl peroxide. Mix thoroughly

c. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Example 5 – Combinations of liquid or liquid and solid surfactants plus stearyl alcohol as foam adjuvant without polymeric agent

Liquid surfactants do not affect viscosity, whereas solid surfactants increase viscosity by adding bulk to improve the quality of the foam.

a) liquid surfactants only with stearyl alcohol

	023	027
chemical name		
Polysorbate 60		3.50
Polysorbate 20	3.00	2.00
sorbitan laurate (span 20)	3.00	
Stearyl alcohol	2.00	3.00
Purified water	86.0	85.5
Benzoyl Peroxide	6.0	6.0
Control:	100.00	100.00
Propellant (AP-70)	8.00	8.00
Results		
QUALITY	G-E	G-E
COLOR	W	W
ODOR	NO ODOR	NO ODOR
SHAKABILITY	GOOD	GOOD
Density		

b) Liquid and solid surfactants only with stearyl alcohol

	028	029	030	031	033
chemical name					
Propylene glycol				3.00	
Polysorbate 60	3.00				
Polysorbate 20	2.00	3.60	3.60	3.60	2.50
Ceteth 20	1.00				
sorbitan laurate (span 20)		1.60	1.60	1.60	1.40
PEG 100-stearate	2.00	2.10	2.10	2.10	2.10
Stearyl alcohol	4.00	10.00	7.00	4.00	2.00
Purified water	82.0	76.7	79.7	79.7	86
Benzoyl Peroxide	6.0	6.0	6.0	6.0	6.0
Control:	100.00	100.00	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00	8.00	8.00
Results					
Viscosity (PFF)		116.98			
Quality	G-E	G-E	G-E	G-E	G-E
Color	W	W	W	W	W
Odor	NO ODOR	NO ODOR	NO ODOR	NO ODOR	NO ODOR
Shakability	GOOD	GOOD	GOOD	GOOD	GOOD
Density		0.052			
Bubble size (μm)		101			
Bubble size (above 500 μm)		4.0			
Collapse time (sec.)		>300/G			

[0305] Comments: Various formulations were explored with different surfactants and amounts of stearyl alcohol without polymer. The formulations contained at least one liquid surfactant and resulted in good to excellent quality foam.

Manufacturing procedure (all formulations in example 5a & 5b)

- a. Add all ingredients to water at 50-60C while vigorously stirring to complete dissolution.
- b. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- c. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Example 6 - Over about 70% water plus Cetylstearyl alcohol an emollient foam adjuvant, and surfactants with and without 10% silicone and 0.5% polymer

	034	040
chemical name		
cyclomethicone		10.00
Polysorbate 60		3.10
Polysorbate 20	3.00	
sorbitan laurate (span 20)	1.50	
sorbitan stearate (span 60)		2.90
PEG 100-stearate	2.00	
Glyceryl stearate		1.00
Cetostearyl alcohol	4.00	2.00
Hydroxypropyl methylcellulose (Methocel K100M)		0.25
Xanthan gum		0.25
Purified water	83.50	74.5
Benzoyl Peroxide	6.0	6.0
Control:	100.00	100.00

	034	040
Propellant (AP-70)	8.00	8.00
Results		
Viscosity (PFF)	6142.69	
QUALITY	G-E	G-E
COLOR	W	W
ODOR	NO ODOR	NO ODOR
SHAKABILITY	GOOD	GOOD
Density	0.033	
Bubble size (µm)	226	
Bubble size (above 500µm)	3.8	
Collapse time (sec.)	>300/G	

[0306] Comments: The formulations contained at least an emollient foam adjuvant, and a surfactant and resulted in good to excellent quality foam with and without a silicone. Polymer was added with the silicone to improve stability.

Manufacturing procedure (034)

- a. Add all ingredients to water at 50-60C while vigorously stirring to complete dissolution.
- b. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- c. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (040)

Step 1: Preparation of Oily Phase (A)

Heat all ingredients to 65C to complete dissolution.

Step 2: Preparation of Water Phase (B)

Add Methocel K100M to water at 5-20C while vigorously mixing. Heat to 60C and Add Xanthan gum while mixing. Add polysorbate 80.

Step 3: Preparation of PFF

Add A to B while mixing. Cool to 40C. Add Cyclomethicone. Cool to RT

Add Benzoyl peroxide. Mix thoroughly while cooling with ice.

Add water if necessary to obtain the correct weight.

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Example 7 – 5% Jojoba a liquid wax and high Klucel with about 79% water

	024	025
chemical name		
Jojoba Oil	5.00	5.00
Polysorbate 60	0.50	
sorbitan stearate (span 60)	2.50	
sorbitan palmitate (span 40)		3.00
Klucel EF	7.00	7.00
Purified water	79.0	79.0
Benzoyl Peroxide	6.0	6.0
Control:	100.00	100.00
Propellant (AP-70)	8.00	8.00
Results		
Viscosity (PFF)	1152.75	1190.75
QUALITY	G-E	G-E
COLOR	W	W
ODOR	NO ODOR	NO ODOR
SHAKABILITY	GOOD	GOOD
Density	0.052	0.05
Collapse time (sec.)	>300/G	
FTC		

	024	025
Foam quality	G	G
Color	White	White
Odor	very faint odor	very faint odor
Shakability	good	good

[0307] Comments: Jojoba oil is a liquid wax with sebum like qualities. Good quality foam was produced with high polymer levels and jojoba and different surfactants.

Manufacturing procedure (024, 025)

Step 1: Preparation of Oil Phase(A)

Mix the Jojoba Oil and Span 60 and Heat up to 60-65C

Step 2: Preparation of Water Phase(B)

Add other ingredients (besides BPO) to water at 60-65C while vigorously stirring till complete dissolution.

Step 3: Preparation of Emulsion (PFF)

Add the water phase to the oily phase while vigorously stirring at 60-65C

Step 4: BPO Addition.

Cool to RT and Add Benzoyl peroxide. Mix thoroughly
add water if necessary to obtain the correct weight.

Step 5: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 6: Pressurizing

Canisters are filled with 8% propellant.

Example 8 – 5% PG and high levels of polymer (Klucel) with about 90% water

	026
chemical name	
Propylene glycol	5.00
Polysorbate 20	2.00
Klucel EF	7.00
Purified water	80.00
Benzoyl Peroxide	6.00
Control:	100.00
Propellant (AP-70)	8.00
Results	
Viscosity (PFF)	209.96
QUALITY	G-E
COLOR	W
ODOR	NO ODOR
SHAKABILITY	GOOD
Density	0.034
Collapse time (sec.)	150/FG

[0308] Comments: It was possible to produce good to excellent quality foam in the presence of PG (a penetration enhancer) with high levels of polymer albeit with a shorter collapse time.

Manufacturing procedure (026)**Step 1: Preparation of Water Phase**

- a. Add Klucel EF to water at 40C while vigorously stirring.
- B. Add Propylene glycol and Polysorbate 20 while stirring.
- c. Cool to RT and Add Benzoyl peroxide. Mix thoroughly
- d. add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Example 9 – Over about 90% water and 7% cocoglycerides an emollient with some emulsifying properties with and without a foam adjuvant

	035	037
chemical name		
Cocoglycerides	7.00	7.00
Polysorbate 80	2.00	2.50
sorbitan oleate (span 80)	5.00	4.50
Glyceryl stearate		1.00
Sodium Carboxymethyl cellulose (30000)	0.50	0.50
Purified water	79.50	78.50
Benzoyl Peroxide	6.0	6.0
Control:	100.00	100.00
Propellant (AP-70)	8.00	8.00
Results		
Viscosity (PFF)		13197.18
QUALITY	FG	G
COLOR		W
ODOR		v.f.od
SHAKABILITY		GOOD
Density		0.072
Bubble size (µm)		270
Bubble size (above 500µm)		3.7
Collapse time (sec.)		>300/G

[0309] Comments: Cocoglyceride is an emollient with surfactant-like properties (semi-surfactant). Addition of glyceryl stearate to the cocoglycerides formulation with sodium CMC resulted in improving the foam quality to good foam with a collapse time in excess of 5 minutes.

Manufacturing procedure (035, 037)**Step 1: Preparation of Oily Phase (A)**

Heat all ingredients to 65C to complete dissolution.

Step 2: Preparation of Water Phase (B)

Heat water to 65C. Add Sodium Carboxymethyl cellulose while vigorously mixing

Step 3: Preparation of PFF

Add A to B while mixing. Cool to RT

Add Benzoyl peroxide. Mix thoroughly while cooling with ice.

Add water if necessary to obtain the correct weight.

Step 4: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 5: Pressurizing

Canisters are filled with 8% propellant.

Example 10- Over about 70% water and 10/11% silicone with polymer

	038	039	040
chemical name			
cyclomethicone	11.00	10.00	10.00
Polysorbate 60		2.40	3.10
Polysorbate 80	3.00		
sorbitan stearate (span 60)		3.60	2.90
sorbitan oleate (span 80)	4.40		
Glyceryl stearate	1.00	1.50	1.00
Cetostearyl alcohol			2.00
Sodium Carboxymethyl cellulose (30000)	0.50		

	038	039	040
Hydroxypropyl methylcellulose (Methocel K100M)		0.25	0.25
Xanthan gum		0.25	0.25
Purified water	74.1	76.0	74.5
Benzoyl Peroxide	6.0	6.0	6.0
Control:	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00
Results			
QUALITY	FG	G-E	G-E
COLOR		W	W
ODOR		NO ODOR	NO ODOR
SHAKABILITY		GOOD	GOOD

[0310] Comments: The combination of Methocel/xanthan gum appeared to be more effective than a single polymer sodium CMC with 10% volatile silicone.

Manufacturing procedure (038)

Step 1: Preparation of Oily Phase (A)

Heat all ingredients to 65C to complete dissolution.

Step 2: Preparation of Water Phase (B)

Heat water to 65C. Add Sodium Carboxymethyl cellulose while vigorously mixing Add polysorbate 80.

Step 3: Preparation of PFF

Add A to B while mixing. Cool to RT

Add Benzoyl peroxide. Mix thoroughly while cooling with ice.

add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (039, 040)**Step 1: Preparation of Oily Phase (A)**

Heat all ingredients to 65C to complete dissolution.

Step 2: Preparation of Water Phase (B)

Add Methocel K100M to water at 5-20C while vigorously mixing. Heat to 60C and Add Xanthan gum while mixing. Add polysorbate 80.

Step 3: Preparation of PFF

Add A to B while mixing. Cool to 40C. Add Cyclomethicone. Cool to RT
Add Benzoyl peroxide. Mix thoroughly while cooling with ice.
add water if necessary to obtain the correct weight.

Step 2: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 3: Pressurizing

Canisters are filled with 8% propellant.

SECTION B**Example 11- Non oleaginous formulation with and without a moisturizing complex of glycerin and sodium pCA**

	004	006	011	014
BPO	6	6	6	6
Cyclomethicone	1	1	1	1
Steareth-21	-	2	2	-
Steareth-2	-	3	3	-
PEG-40 Stearate	3	-	-	3
Polysorbate 60	1	-	-	1
Glyceryl monostearate	1	1	1	1
Stearyl alcohol	1	1	1	1
Sodium CMC	1	1	-	-
Xanthan gum	-	-	0.35	0.35
Methocel K100	-	-	0.35	0.35
Citric acid	0.31	0.31	0.31	0.31
Sodium Citrate	0.44	0.44	0.44	0.44
Glycerin	8	-	8	-
Sodium PCA	2	-	2	-
Purified water	75.25	84.25	74.55	85.55

	004	006	011	014
Propellant	AP-70	AP-70	AP-70	1681
PFF				
Centrifugation 3k (%)	20% sedim	-	-	10% sedim
Centrifugation 10k (%)	20% sedim	-	20% sedim	20% sedim
Viscosity (PFF) (cps)	5575	-	24864	6818
Microscopic observation	agglom.	-	agglom	agglom
pH direct	4.61	-	4.49	4.37
Foam				
Foam Quality	G	FG	G	G
Density (g/mL)	0.036	-	-	-
Shakability	1	0	0	1
Collapse Time	>300/FG	-	>300/G	>300/FG

[0311] Comments: Replacing the surfactant system stearate21/stearate2 with PEG 40 Stearate and Polysorbate 60 improved the shakability of the formulations. The quality of the formulations with xanthan/Methocel appeared to be better. The presence of glycerin/sodium PCA may also help. The suspended BPO as expected precipitated on centrifugation (agglom = agglomeration). The moisture agents (glycerin and sodium PCA) affect the properties of the formulation, however, such moisture agents are preferred in a formulation containing BPO because BPO has a drying effect on skin.

Manufacturing procedure (004, 006-w/o 4.1)

Step 1: Preparation of Water Phase (B)

1.1. Heat water to 65-70°C, add slowly CMC while vigorously stirring

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Add Benzoyl peroxide and homogenize 15 minutes

Step 6 : pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5 ± 0.2 .
- 6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (011, 014-w/o 4.1)

Step 2: Preparation of water Phase (B)

- 1.1. Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.
- 1.2. Heat (Step 1.1) to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.
- 1.3. Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.
- 6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 12 - Oleaginous formulation of 6% mineral oil with and without a moisturizing complex of glycerin and sodium pCA

	005	007	008	012	013
BPO	6	6	6	6	6
Mineral oil	6	6	6	6	6
Cyclomethicone	1	1	1	1	1
Steareth-21	-	-	-	2	2
Steareth-2	-	-	-	3	3
PEG-40 Stearate	3	3	3	-	-
Polysorbate 60	1	1	1	-	-
Glyceryl monostearate	1	1	1	1	1
Stearyl alcohol	1	1	1	1	1
Sodium CMC	0.5	1	-	0.5	-
Xanthan gum	-	-	0.35	-	0.35
Methocel K100	-	-	0.35	-	0.35
Citric acid	0.31	0.31	0.31	0.31	0.31
Sodium Citrate	0.44	0.44	0.44	0.44	0.44

Glycerin	8	8	8	-	-
Sodium PCA	2	2	2	-	-
Purified water	69.75	69.25	69.55	78.75	78.55
Propellant	AP-70		AP-70	AP-70	AP-70
PFF					
Centrifugation 3k (%)	-	15% sedim	10% sedim	-	-
Centrifugation 10k (%)	-	15% sedim	20% sedim 20% cream	20% sedim	20% sedim
Viscosity (PFF) (cps)	-	-	6218	-	30486
Microscopic observation	-	agglom	agglom	-	no agglom
pH direct	-	4.59	4.48	4.60	4.60
Foam					
Foam Quality	FG	G	G	G-	G
Density (g/mL)	-	-	0.034	-	-
Shakability	2	1	1	0	0
Collapse Time	-	-	>300/FG	-	60/F

[0312] Comments: By increasing the amount of polymer the foam quality was improved and good quality foam was achieved. The formulations with the moisturizing complex were shakable. In contrast the formulations without the moisturizing complex had poor or no shakability but were flowable. : Replacing the surfactant system stearate21/stearate2 with PEG 40 Stearate and Polysorbate 60 improved the shakability of the formulations.

Manufacturing procedure (005, 007, 012-w/o 4.1)

Step 1: Preparation of Water Phase (B)

1.1. Heat water to 65-70°C, add slowly CMC while vigorously stirring using paddle stirrer.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6 : pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH to obtain a pH of 4.5 ± 0.2 .
- 6.2. add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (008, 013-w/o 4.1)

Step 1: Preparation of Water Phase (B)

- 1.4. Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.
- 1.5. Heat to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.
- 1.6. Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

- 2.2. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.4. Add the oil phase to the water phase at 65 - 70°C with agitation using 4-blade impeller.

3.5. Agitation continues until PFF uniformity is reached.

3.6. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.

4.2. Cool to RT and not more than 30°C.

4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization and Benzoyl Peroxide addition

5.1. Start homogenization while cooling with ice bath. Add Benzoyl peroxide and keep homogenisation for 15 minutes.

Step 6: pH adjustment

6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

6.2. add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 13 - Oleaginous formulation with 6% MCT with and without a moisturizing complex of glycerin and sodium pCA

	009	010	015	016
BPO	6	6	6	6
MCT oil	6	6	6	6
Cyclomethicone	1	1	1	1
Steareth-21	-	2	2	-
Steareth-2	-	3	3	-
PEG-40 Stearate	3	-	-	3
Polysorbate 60	1	-	-	1
Glyceryl monostearate	1	1	1	1
Stearyl alcohol	1	1	1	1
Sodium CMC	-	0.5	-	0.5
Xanthan gum	0.35	-	0.35	-
Methocel K100	0.35	-	0.35	-

Citric acid	0.31	0.31	0.31	0.31
Sodium Citrate	0.44	0.44	0.44	0.44
Glycerin	-	8	8	-
Sodium PCA	-	2	2	-
Purified water	79.55	68.75	68.55	79.75
Propellant	AP-70	AP-70	AP-70	AP-70
PFF				
Centrifugation 3k (%)	10% sedim	-	-	20% sedim
Centrifugation 10k (%)	10% sedim	10% sedim	20%sedim	20% sedim 40% cream
Viscosity (PFF) (cps)	6423	20183	-	-
Microscopic observation	no agglom	agglom	agglom	agglom
pH direct	4.30	4.57	4.46	4.39
Foam				
Foam Quality	G	G-	G	G
Density (g/mL)	-	-	-	-
Shakability	1	0	0	2
Collapse Time	>300/G	30/F	>300/G	>300/FG

[0313] Comments: When mineral oil was replaced by MCT then surprisingly the position was reversed with the moisturizing complex instead had poor shakability. Good quality foam was achieved.

Manufacturing procedure (009)

Step 1: Preparation of Water Phase (B)

- 1.1. Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed. The temperature should not exceed 10-15 °C.
- 1.2 Heat to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.
- 1.3 Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to RT and not more than 30°C.

Step 4: Buffer addition

4.1. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6 : pH adjustment

6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

6.2. add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (010)**Step 1: Preparation of Water Phase (B)**

1.1. Heat water to 65-70°C, add CMC while vigorously stirring.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Add Benzoyl peroxide and homogenize for 15 minutes at 8000 RPMs while cooling with ice bath.

Step 6 : pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.
- 6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (015)**Step 1: Preparation of Water Phase (B)**

- 1.1 Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed.
- 1.2 Heat to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.

1.3 Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.

4.2. Cool to RT and not more than 30°C.

4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6 : pH adjustment

6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5 ± 0.2 .

6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (016)**Step 1: Preparation of Water Phase (B)**

1.1. Heat water to 65-70°C, add slowly CMC while stirring.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to RT and not more than 30°C.

Step 4: Buffer addition

4.1. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6 : pH adjustment

6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 14 – Oleaginous placebo oil/silicone containing formulations with and without a moisturizing complex of glycerin and sodium pCA

Treatment	1	2	3	4	5	6
Formulation	BPO-008-071126P	BPO-016-071126P	BPO-invest-042-071125P	BPO-014-071126P	BPO-invest-041-071125P	BPO-invest-043-071126P
Mineral oil	6.00	-	6.00	-	-	-
MCT oil	-	6.00	-	-	-	6.00
Cyclomethicone	1.00	1.00	1.00	1.00	1.00	1.00
PEG-40 Stearate	3.00	3.00	3.00	3.00	3.00	3.00
Polysorbate 60	1.00	1.00	1.00	1.00	1.00	1.00
Glyceryl monostearate	1.00	1.00	1.00	1.00	1.00	1.00
Stearyl alcohol	1.00	1.00	1.00	1.00	1.00	1.00
Hydroxypropyl methylcellulose	0.35	-	0.35	0.35	0.35	-
Xanthan gum	0.35	-	0.35	0.35	0.35	-
Sodium CMC	-	0.50	-	-	-	0.50
Purified water	75.55	85.75	85.55	91.55	81.55	75.75
Glycerin	8.00	-	-	-	8.00	8.00
Sodium PCA	2.00	-	-	-	2.00	2.00
Citric acid	0.31	0.31	0.31	0.31	0.31	0.31
Sodium citrate tribasic dehydrate	0.44	0.44	0.44	0.44	0.44	0.44
Control:	100.00	100.00	100.00	100.00	100.00	100.00
Propellant (AP-70)	8.00	8.00	8.00	8.00	8.00	8.00

[0314] Comments: The advantages of formulations with and without the moisturizing complex glycerin/pCA were explored with and without mineral oil or MCT oil. Chemical stability results with and without the moisturizing complex are shown below in Example 24.

Manufacturing procedure for treatment 1, 2 and 4-describe in section B (just without B)

Manufacturing procedure (041)

Step 1: Preparation of Water Phase (B)

1.1.Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed. The temperature should not exceed 10-15°C.

1.2.Heat to 50°C slowly, add Xanthan gum with vigorous mixing. Keep temperature at 70.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Start homogenization and keep homogenization for 15 minutes.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.
- 6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (042)**Step 1: Preparation of Water Phase (B)**

- 1.1. Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing

until homogeneous and no particles are observed. The temperature should not exceed 10-15 °C.

1.2 Heat to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.

1.3 Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool to RT.

Step 4: Buffer Addition

4.1. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

5.1. Homogenize for 15 minutes

Step 6: pH adjustment

6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Manufacturing procedure (043)**Step 1: Preparation of Water Phase (B)**

- 1.1. Heat water to 65-70°C, add slowly CMC while vigorously stirring using paddle stirrer.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
3.2. Agitation continues until PFF uniformity is reached.
3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerine and sodium PCA to the emulsion while mixing thoroughly.
4.2. Cool to RT and not more than 30°C.
4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Start homogenization and keep homogenization for 15 minutes.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.
6.2. add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 15 – Placebo formulations without BPO

Order of Appearance in Corneometer Study Figs	4	2	1	5	3	6
	014P	016P	008P	041P	042P	043P
Mineral oil			6.00		6.00	
MCT oil		6.00				6.00
Cyclomethicone	1.00	1.00	1.00	1.00	1.00	1.00
PEG-40 Stearate	3.00	3.00	3.00	3.00	3.00	3.00
Polysorbate 60	1.00	1.00	1.00	1.00	1.00	1.00
Glyceryl monostearate	1.00	1.00	1.00	1.00	1.00	1.00
Stearyl alcohol	1.00	1.00	1.00	1.00	1.00	1.00
Hydroxypropyl methylcellulose	0.35		0.35	0.35	0.35	
Xanthan gum	0.35		0.35	0.35	0.35	
Sodium CMC		0.50				0.50
Purified water	91.55	85.75	75.55	81.55	85.55	75.75
Glycerin			8.00	8.00		8.00
Sodium PCA			2.00	2.00		2.00
Citric acid	0.31	0.31	0.31	0.31	0.31	0.31
Sodium citrate tribasic dehydrate	0.44	0.44	0.44	0.44	0.44	0.44
Control:	100.00	100.00	100.00	100.00	100.00	100.00
Propellant (ap-70)	8.00	8.00	8.00	8.00	8.00	8.00

Results						
PFF						
Viscosity (PFF)	2290.51	445.91	1628.65	2388.49	2025.57	455.90
Centrifugation 3k	stable	80% Creaming	stable	stable	stable	75% Creaming
Centrifugation 10k	15% Creaming	30% Creaming	20% Creaming	10% Creaming	20% Creaming	25% Creaming
Ph Undiluted	4.45	4.53	4.59	4.49	4.37	4.64
Foam						
Quality	E	E	E	E	E	E
Color	White	White	White	White	White	White
Odor	No odor	Very faint odor	No odor	Very faint odor	No odor	Very faint odor
Shakability	1	2	2	1	2	2
Density	0.033	0.033	0.035	0.033	0.036	0.039
Collapse Time	>300/G	>300/FG	>300/FG	>300/G	>300/G	>300/G

[0315] Comments: All the formulations produced excellent quality foam with low density and good collapse time. All were resistant to centrifugation at 3K with only two formulations showing some creaming but no phase separation. All of the formulations were stable following centrifugation, indicating physical stability of the formulations. To determine which formulations would be compatible with human skin, studies were carried out to determine the skin-hydration effect of the formulations (see Example 16).

Example 16 – A Double-Blind Study Of The Skin-Hydration Effect Of Glycerin Sodium PCA vehicle of Example 14

[0316] Healthy subjects were applied with single dose of formulations as shown in Example 14 . Skin hydration is measured using a Corneometer® CM 825 instrument. (Courage+Khazaka, Koln, Germany). The measuring principle of the Corneometer® CM 825 is based on capacitance measurement of dielectric medium. Any change in the dielectric constant due to skin surface hydration alters the capacitance of a measuring capacitor. It is capable of detecting even slight changes in the skin hydration level.

[0317] Study Flow chart is shown below:

STUDY ACTIVITY	Baseline*	6 hours	7 hours
Inclusion/exclusion criteria	X		
Application of the test preparations	x		
Assessment of skin hydration		X	X
Assessment of tolerability parameters and Adverse Events		X	X

[0318] Skin hydration level is assessed at baseline (fifteen minutes after each subject washed the left and right forearms) with the Corneometer® CM 825. The formulations are applied in designated chambers under occlusion for 6 hours which are then removed and the skin cleaned. Hydration is then measured one hour later.

[0319] Study protocol: The study was performed in a temperature controlled room (20-24°C). Subjects washed their arms with water (no soap) and dried their arms with dry paper towel. Formulations were applied using test chambers. The location of each chamber within the stripe was marked once applied (maximum of

3 stripes on each arm). Each stripe contained only one formulation. One stripe served as a control, non treated area. Three replicates of each formulation were applied. Formulations, control products and control non treated areas were randomly assigned to the treatment sites according to a randomization list, provided by the study statistician. The application array was unknown to the study operator and subjects. An amount of approximately 4 mg (40ul) of each of the study formulations was applied on the treatment sites as described by the randomization list. Skin hydration level was assessed at baseline T=0 (minimum 15 minutes following rinse), using the Corneometer® CM 825, and tested based on study design.

[0320] As shown in Figures 3-5, the formulations with glycerin/pCA have a substantial moisturizing effect when compared with the formulations lacking this combination. This is mostly beneficial since benzoyl peroxide is known to cause undesired side effects such as skin dryness and irritation.

Example 17 – Short Stability Study

Ingredients	008	014	016
BPO	6	6	6
Mineral oil	6	-	-
MCT oil	-	-	6
Cyclomethicone	1	1	1
PEG-40 Stearate	3	3	3
Polysorbate 60	1	1	1
Glyceryl monostearate	1	1	1
Stearyl alcohol	1	1	1
Sodium CMC	-	-	0.5
Xanthan gum	0.35	0.35	-
Methocel K100	0.35	0.35	-
Citric acid	0.31	0.31	0.31
Sodium Citrate	0.44	0.44	0.44
Glycerin	8	-	-
Sodium PCA	2	-	-
Purified water	69.55	85.55	79.75
Propellant (propane, isobutane, butane)	8	8	8

	008 (PFF)	008 (pressurized formulation)	014 (PFF)	014 (pressurized formulation)	016 (PFF)	016 (pressurized formulation)
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API content (% w/w)	T-0	5.86	5.68	5.96	6.06	6.03	6.13
	2 Weeks / 40°C	5.65	5.57	5.75	5.62	5.86	5.32
Degradation			1.94%		7.26%		13.2%

[0321] Comments: Unexpectedly, the chemical stability of foamable compositions containing benzoyl peroxide appears to be significantly enhanced by adding moisturizing complex such as glycerin/pCA to the compositions. (Note in Example 17 the analytical method used BPO as a reference standard.)

[0322] So far as physical stability is concerned all these formulations without carbopol were homogenous on preparation but were found to separate over time. On shaking the separated formulations resuspended and were visually homogenous. In contrast, formulations with added carbopol, seen below in Example 23, remained homogenous for 6 months save that where some creaming was observed the creaming was readily reversible on shaking.

SECTION C

Example 18A -Comparison between BPO formulation with and without Carbopol

1. Formulations

Ingredients	BPO-025	BPO-032
Cyclomethicone	1.00	1.00
PEG-40 Stearate	3.00	3.00
Polysorbate 60	1.00	1.00
Glyceryl monostearate	1.00	1.00
Stearyl alcohol	1.00	1.00
Carbomer 934P (Carbopol 974P)	-	0.35
Hydroxypropyl methylcellulose	0.50	0.27
Xanthan gum	0.50	0.27
Citric acid	0.31	0.38
Sodium citrate tribasic dihydrate	0.44	0.59
Hydrous benzoyl peroxide	6.00	6.00
Trolamine	-	0.18
Purified water	to 100	to 100
Propellant (AP-70)	8	8
Results	BPO 025 (To)	BPO 032 (To)
Shakability	Moderate	2

Foam Quality	Good	E
Foam Color	White	white
Foam Odor	No Odor	no odor
Density (mg/ml)	N\M*	0.034
pH diluted (1:5)	N\M*	4.50
Collapse Time (sec)	>300	>300
Expansion Time (sec)	N\M*	50

N\M*-Not Measured

[0323] Comments: In formulations (BPO-032, 035, 042, 047, 048) carbomer was added to hydroxypropylmethylcellulose and xanthan polymers, whose concentrations were in parallel reduced. Carbomer is a suspending agent and thickener. The unexpected advantage of this material is well observed in the homogeneity test (visual test). In formulation BPO-025 which does not have carbomer, migration of the particles to the bottom of the pressurized glass bottle can be seen in FIG 15. In clear contrast in formulation BPO-032 which includes 0.35% carbomer, this phenomenon is not observed. Formulation BPO-032 as well as all other carbomer optimized formulation, looks homogeneous in particles aspect. **FIG 15** shows the effect of the presence and absence of carbomer after about 6 month at 25°C. The unexpected difference in homogeneity can be ascribed the addition of the buffered carbomer. It may be without being bound by any theory that somehow in the low viscous formulations the carbomer can maintain a fluid structural relationship with BPO which allows it to remain homogeneous even over time.

2. Procedure:

- a) (BPO32).** See Example 23, part A for detailed procedure. In general terms where carbomer is used, base is added at the beginning to swell the polymer to form a gel. Subsequently after the oil phase is mixed with the aqueous phase to form a gel emulsion. The buffer (or pH adjuster) is added at the end of the procedure to produce a fluid low viscous emulsion to which the propellant is ultimately added.

b) (BPO025)**Step 1: Preparation of Water Phase (B)**

- 1.1 Heat 70g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2 Cool to 50°C and add Xanthan gum with vigorous mixing
- 1.3 Heat to 70°C

Step 2: Preparation of Phase A

- 2.1. Heat all ingredients of phase A to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add phase A to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool to RT and not more than 30°C.
- 3.4. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 25g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion (from step 5) is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 18B -Comparison between 1% BPO formulation and 15% BPO formulation with carpopol

phase		BPO-47-1 (1%)	BPO-47-15 (15%)
A	Light mineral oil	6.00	6.00
	Cyclomethicone	1.00	1.00
	PEG-40 Stearate	3.00	3.00
	Polysorbate 60	1.00	1.00
	Glyceryl monostearate	1.00	1.00
	Stearyl alcohol	1.00	1.00
B	Carbopol 981 solution	0.50	0.50
	Hydroxypropyl methylcellulose	0.20	0.20
	Xanthan gum	0.20	0.20
	Glycerin	8.00	8.00
	Sodium PCA	2.00	2.00
	Citric acid	0.38	0.38
	Sodium citrate tribasic dihydrate	0.59	0.59
	Benzoyl peroxide	1.00	15.00
	Sodium hydroxide 18% solution	0.50	0.50
	Purified water	to 100	to 100
	Propellant	8.00	8.00
	Results:		
	Quality	E	E
	Color	white	white
	Odor	no odor	no odor
	Shakability	2	2
	Collapse Time	>180	>180
	Microscopic observation	crystals observed uniformity	crystals observed uniformity
	Bubble size	71	91
	Viscosity (PFF)	1279.73	6558.6
	viscosity+ 8% pentane	884.81	6494.62
	% ratio viscosity between the foamable formulation with 8% pentane and the pre- foam formulation without pentane	69.14	99.02

Procedure (for 1% and 15%):**Step 1: Preparation of Water Phase (B)**

- 1.2. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). In this formulation the base was sodium hydroxide. Heat carbomer solution and heat to 70°C. Add methocel with vigorous mixing.
- 1.3. Cool step 1.1 to 50°C and add Xanthan gum with vigorous mixing.
- 1.4. Heat step 1.2 to 70°C

Step 2: Preparation of Oil Phase (A)

- 2.2. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to RT and not more than 40°C.
- 3.4. Add glycerin and sodium PCA to the emulsion while mixing thoroughly.
- 3.5. Cool to RT and not more than 30°C.
- 3.6. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 28g water and mix.
- 4.2. Add to step 3 and mix.
- 4.3. Check pH.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.
- 6.2. Add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

[0324] Comments: Both 1% and 15% BPO formulations achieved excellent, shakable non-breakable and uniform foam. These formulations were identical except for the amount of water and BPO present. In the high BPO formulation the water was 14% less. Increasing BPO's concentration dramatically caused an increase of the viscosity of the PFF. The viscosity remained high even when diluted with 8% pentane (a low volatile hydrocarbon) to simulate the volatile hydrocarbon propellants.

Example 19 -10% BPO

a) Comparison results between mineral oil emulsion formulations with different polymeric combinations.

phase	Ingredients	BPC-054	BPC-061
A	Mineral oil	6.00	6.00
	Cyclomethicone	1.00	1.00
	PEG-40 Stearate	3.00	3.00
	Polysorbate 60	1.00	1.00
	Glyceryl monostearate	1.00	1.00
	Stearyl alcohol	1.00	1.20
B	Carbomer 941 (Carbopol 981)	-	0.25
	Carbomer 940 (Carbopol 980)	0.30	-
	Crospovidone CL-M	1.00	-
	Hydroxypropyl methylcellulose	0.10	0.10
	Xanthan gum	0.10	0.10
	Glycerin	8.00	8.00
	Sodium PCA	2.00	2.00
	Citric acid	0.38	0.38
	Sodium citrate tribasic dihydrate	0.59	0.59
	Hydrous benzoyl peroxide	10.00	10.00
	Sodium hydroxide 18% solution	0.30	0.25
	Purified water	to 100	to 100
	Propellant (AP-70)	8.00	8.00
	Results:		
	Quality	E	G+
	Color	white	white
	Odor	no odor	no odor

phase	Ingredients	BPC-054	BPC-061
	Shakability	1	1
	Density	0.042	0.037
	Collapse Time	>300	>300
	pH diluted	4.65	4.62

[0325] Comments: Using a combination of a gelling agent, (Carbomer 940 (Carbopol 980) and a dispersing agent (Crospovidone CL-M) achieved excellent, shakable non-breakable foam. Changing gelling agent with much lower viscosity and dropping dispersing agent, caused a minimal decreasing to foam quality. Both formulations also had hydroxypropyl methylcellulose and xanthan present.

Procedure (for BPC054):

Step 1: Preparation of Water Phase (B)

- 1.1. Heat part of water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Heat Carbomer solution to 50°C while mixing.
- 1.3. Add step 1.1 to 1.2 and mix until no clumps are detected.
- 1.4. Adjust step 1.3 to 50°C and add Xanthan gum with vigorous mixing
- 1.5. Heat step 1.4 to 70°C
- 1.6. Heat another part of water to 70°C
- 1.7. Add crospovidone to step 1.6 and mix.
- 1.8. Add step 1.7 to step 1.5 and mix.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to RT and not more than 40°C.
- 3.10 Add glycerin and sodium PCA to the emulsion while mixing thoroughly.

Cool to RT and not more than 30°C. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 8g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. Add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5 ± 0.2 .

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Procedure (for BPC056):

Step 1: Preparation of Water Phase (B)

- 1.1. Heat 125g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Add carbomer solution and mix until thoroughly wetted and evenly dispersed, no clumps are detected
- 1.3. Cool step 1.2 to 50°C and add Xanthan gum with vigorous mixing
- 1.4. Heat step 1.3 to 70°C
- 1.5. Heat 30g water to 70°C
- 1.6. Add crospovidone to step 1.5 and mix.
- 1.7. Add step 1.6 to step 1.4 and mix.

Step 2: Preparation of Oil Phase (A)

2.1 Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

3.1. Add slowly the oil phase to the water phase at 65 - 70°C with agitation

3.2. Agitation continues until PFF uniformity is reached.

3.3. Cool the emulsion to RT and not more than 30°C.

3.4. Check pH.

Step 4: Buffer addition

4.1. Add Citric acid and sodium citrate tribasic dihydrate to 17.5g water and mix.

4.2. Add step 4.1 to step 3 and mix. Check pH.

4.3 add water if necessary to obtain the correct weight.

Step 5: Benzoyl Peroxide addition and Milling

5.1. Place about ¼ of PFF quantity to the vessel while cooling with 10°C external water bath and add slowly Benzoyl Peroxide to the PFF while mixing.

5.2. Add the PFF left to the vessel while mixing Continue mixing until uniformity

Step 6: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 7: Pressurizing

Canisters are filled with 8% propellant.

b) Comparison results between formulations without mineral oil containing 10% BPO

Ingredients	BPC-057	BPC-053	BPC-060
Cyclomethicone	1.00	1.00	1.00
PEG-40 Stearate	3.00	3.00	3.00
Polysorbate 60	1.00	1.00	1.00
Glyceryl monostearate	1.00	1.00	1.00
Stearyl alcohol	1.20	1.00	1.10
Carbomer 934P (Carbopol 974P)	-	0.35	-
Carbomer 941 (Carbopol 981)	-	-	0.20
Carbomer 940 (Carbopol 980)	0.25	-	-

Crospovidone CL-M	1.00	-	1.00
Hydroxypropyl methylcellulose	0.10	0.15	0.15
Xanthan gum	0.10	0.15	0.15
Glycerin	8.00	-	-
Sodium PCA	2.00	-	-
Citric acid	0.38	0.38	0.38
Sodium citrate tribasic dihydrate	0.59	0.59	0.59
Hydrous benzoyl peroxide	10.00	10.00	10.00
Trolamine	-	0.18	-
Sodium hydroxide 18% solution	0.25		0.20
Purified water	to 100	to 100	to 100
Propellant (AP-70)	8.00	8.00	8.00
Results			
Quality	E	G+	G
Color	white	white	white
Odor	no odor	no odor	very faint odor
Shakability	1	1	2
Density	0.033	0.035	0.040
Collapse Time	>300	>300	>300
pH diluted	4.62	4.68	4.59

[0326] Comments: All formulations achieved good to excellent, shakable non-breakable foam. Glycerin and Sodium PCA appeared to have improved foam quality although there are also other small changes between formulations which may have contributed.

Procedure (for BPC053):

Step 1: Preparation of Water Phase (B)

- 1.1 Heat 70g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2 Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Heat carbomer solution to 50°C.
- 1.3 Add step 1.1 to step 1.2 and mix until no clumps are detected.
- 1.4 Adjust step 1.3 to 50°C and add Xanthan gum with vigorous mixing
- 1.5 Heat step 1.4 to 70°C

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool to RT and not more than 30°C.
- 3.4. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 17g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes until uniformity

Step 6: pH adjustment

- 6.1. Verify temperature emulsion (from step 5) is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Procedure (for BPC057):**Step 1: Preparation of Water Phase (B)**

- 1.1. Heat 45g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Heat Carbomer solution to 50°C while mixing.
- 1.3. Add step 1.1 to 1.2 and mix until no clumps are detected.

- 1.4. Adjust step 1.3 to 50°C and add Xanthan gum with vigorous mixing
- 1.5. Heat step 1.4 to 70°C
- 1.6. Heat 30g water to 70°C
- 1.7. Add crospovidone to step 1.6 and mix.
- 1.8. Add step 1.7 to step 1.5 and mix.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to RT and not more than 40°C.
- 3.4. Add glycerin and sodium PCA to the emulsion while mixing thoroughly.
- 3.5. Cool to RT and not more than 30°C.
- 3.6. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 10g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 min. until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Procedure (for BPC060):

Step 1: Preparation of Water Phase (B)

- 1.1 Add to 300g water: methocel, Carbomer, base and Xanthan gum while mixing with Jet impeller for 45 min.
- 1.2 Heat step 1.1 to 70°C
- 1.3 Heat 75g water to 70°C
- 1.4 Add crospovidone to step 1.3 and mix.
- 1.5 Add step 1.4 to step 1.3 and mix.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool to RT and not more than 30°C.
- 3.4. Check pH.
- 3.5. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 4: Benzoyl Peroxide addition and Milling

- 4.1. Place about ¼ of PFF quantity to the vessel while cooling with 10°C external water bath and add slowly Benzoyl Peroxide to the PFF while mixing.
- 4.2. Continue mixing until uniformity and no agglomeration is seen in microscopic observation.

Step 5: Buffer addition

- 5.1. Add NaOH 18% and mix.

5.2. Check pH.

5.3. Add Citric acid and sodium citrate tribasic dihydrate to 10g water and mix.

5.4. Add step 5.1 to step 4 and mix.

5.5. Check pH.

Step 6: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 7: Pressurizing

Canisters are filled with 8% propellant.

Example 20 - Preliminary hydration tests comparing formulations with and w/o carbopol.

Study protocol: See example 16. The procedure adopted is along the lines as described therein.

STUDY ACTIVITY	Baseline*	6 hours	7 hours
Inclusion/exclusion criteria	x		
Application of the test preparations	x		
Assessment of skin hydration		X	X
Assessment of tolerability parameters and Adverse Events		X	X

Treatment ID	Treatment Name	Carbopol 981	Methocel	Xanthan
A	No treatment			
B	BPO 008-081110P	No	Yes	Yes
C	BPO 047-081110P	Yes	Yes	Yes

Conclusions:

[0327] Based on the study results (see Figures 6 and 7), no major hydration difference was observed between the two formulations. The formulation without carbomer was slightly better at 6 hours. Almost no difference was observed at

seven hours. Both formulations increased the hydration of the skin and maintained it significantly higher compared to the control following six and seven hours. One hour after the skin was washed, the hydration effects of the formulations remained higher than controls. Note: Formulation 008 hydration was also previously observed in Example 16. Formulation 008P was presented in Example 15 and formulation 047 with BPO was presented in Example 23, which similar to the placebo formulation used herein except that in the placebo BPO is replaced by water. Both formulations are comprised of polymeric agents, Methocel and Xanthan, however 047 employs lower concentrations and carbopol 047 was added.

Procedure for 047 describes in example 18

Procedure (for BPO008):

Step 1: Preparation of Water Phase (B)

- 1.1. Heat part of water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool the rest of water. Add the hot water to the cool water while mixing until homogeneous and no particles are observed. The temperature should not exceed 10-15 °C.
- 1.2 Heat to 50°C, add Xanthan gum with vigorous mixing. Keep temperature at 70.
- 1.3 Add all other water phase ingredients and heat to 70°C to obtain complete dissolution of all ingredients.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to 40°C.

Step 4: Glycerin, Sodium PCA and buffer addition

- 4.1. Add glycerin and sodium PCA to the emulsion while mixing thoroughly.
- 4.2. Cool to RT and not more than 30°C.
- 4.3. Add Citric acid and sodium citrate tribasic dihydrate to the water and mix.

Step 5: Homogenization

- 5.1. Add Benzoyl peroxide and homogenize for 15 minutes while cooling with ice bath.

Step 6 : pH adjustment

- 6.1. Verify temperature emulsion is less than 30°C. Check pH, to obtain a pH of 4.5 ± 0.2 .
- 6.2. add water if necessary to obtain the correct weight.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Example 21- Comparative Hydration tests for BPO formulation (BPO-047)**with and w/o, glycerin, with and w/o NaPCA and with a combination thereof**

Study protocol: See Examples 16 and 20. The procedure adopted is along the lines as described therein.

STUDY ACTIVITY	Baseline*	6 hours	7 hours
Inclusion/exclusion criteria	x		
Application of the test preparations	x		
Assessment of skin hydration		X	X
Assessment of tolerability parameters and Adverse Events		X	X

Treatment ID	Treatment Name	Glycerin	NaPCA
A	BPO 047- A -081116P	N/A	2.00
B	BPO 047- B -081116P	8.00	N/A
C	BPO 047- C -081116P	2.00	8.00
D	BPO 047- D -081116P	5.00	5.00
E	BPO 047- E -081116P	2.00	5.00
F (reference)	BPO 047--081110P	8.00	2.00
G	No treatment		

Conclusions:

[0328] Based on the results shown in Figures 8 – 10, glycerin is a main contributor to the hydration effect. Sodium PCA at 2% also increases hydration but to a lesser extent compared to 8% glycerin. It may be that higher levels of sodium PCA improve hydration. Increasing sodium PCA at the account of glycerin also resulted in a similar level of improved hydration. It may be that at the combined levels of glycerin and sodium PCA in the presence of mineral oil hydration is maximized which may explain the minor differences between the results.

Example 22- Stability studies formulations and results at and 30°C – A six-month foam Chemical stability of BPO in 30°C-in various formulations comparing to Benzac an existing BPO water based gel product comprising 5% BPO.

Formulation No.	Assay Results at 30°C						
	T-0	2 month	% from T-0	3 month	% from T-0	6 month	% from T-0
BPO-032-080330	6.40	N/M*	0.0	N/M*	N/M*	N/M*	N/M*
BPO-035-080331	6.33	6.34	100.2	6.35	100.2	6.27	99.0
BPO-042-080101	6.27	N/M*	0.0	6.28	100.1	6.33	101.1
BPO-047-080402	6.18	N/M*	0.0	6.36	102.9	6.07	98.2
BPO-048-080403	6.23	N/M*	0.0	6.27	100.8	6.37	102.4
Benzac AC 5% Gel (tube)	5.20	N/M*	0.0	5.40	103.8	5.47	105.2

*-N/M- not measured

Note: Benzac Ingredients: Benzoyl peroxide 5% in a water base gel. Non-medicinal ingredients: Acrylates copolymer, carbomer 940, docusate sodium, edetate disodium, glycerin, poloxamer 182, propylene glycol, purified water, silicon dioxide, and sodium hydroxide. May contain citric acid to adjust pH. Benzac is a gel BPO formulation currently on the market. BPO is in a gel and is not fluid..

[0329] Comments: BPO shows 6-month chemical stability in the different examples tested of the two types of formulations that have been developed at 30°C: emollient (+6% oil) and mineral oil-free.

Example 23- A 6-month foam physical stability of BPO at 25°C and at 30°C with the formulations seen in Example 22

Part A – Formulation 032 (without mineral oil)

Ingredients	BPO-032			
Cyclomethicone	1.00			
PEG-40 Stearate	3.00			
Polysorbate 60	1.00			
Glyceryl monostearate	1.00			
Stearyl alcohol	1.00			
Carbomer 934P (Carbopol 974P)	0.35			
Hydroxypropyl methylcellulose (HPMC-Methocel K100M)	0.27			
Xanthan gum	0.27			
Citric acid	0.38			
Sodium citrate tribasic dihydrate	0.59			
Hydrous benzoyl peroxide	6.00			
Trolamine	0.18			
Purified water	to 100			
Propellant (AP-70)	8.00			
Results	T-0	T-2, 30°C	T-2, 25°C	T-6, 30°C
Shakability	2	1	1	N/M*
Foam Quality	E	G	E	N/M*
Foam Color	white	white	white	N/M*
Foam Odor	no odor	v.f.odor	no odor	N/M*
Density (mg/ml)	0.034	0.030	0.037	N/M*
pH diluted (1:5)	4.50	4.28	4.37	N/M*
Collapse Time (sec)	>300	>300	>300/G	N/M*
Expansion Time (sec)	50	N/M*	N/M*	N/M*

N/M*-not measured

Procedure (BPO032)

Step 1: Preparation of Water Phase (B)

- 1.4 Heat 70g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.5 Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). In this formulation the base was trolamine. Heat carbomer solution to 50°C.

- 1.6 Add step 1.1 to step 1.2 and mix until no clumps are detected.
- 1.7 Adjust step 1.3 to 50°C and add Xanthan gum with vigorous mixing
- 1.8 Heat step 1.4 to 70°C

Step 2: Preparation of Phase A

- 2.2. Heat all ingredients of phase A to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.5. Add phase A to the water phase at 65 - 70°C with agitation
- 3.6. Agitation continues until PFF uniformity is reached.
- 3.7. Cool to RT and not more than 30°C.
- 3.8. Check pH.

Step 4: Buffer addition

- 4.5. Add Citric acid and sodium citrate tribasic dihydrate to 25g water and mix.
- 4.6. Add step 4.1 to step 3 and mix.
- 4.7. Check pH.
- 4.8. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.2. Verify temperature emulsion (from step 5) is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Part B – Formulation 035 (with mineral oil)

Ingredients	BPO-035			
Mineral oil	6.00			
Cyclomethicone	1.00			
PEG-40 Stearate	3.00			
Polysorbate 60	1.00			
Glyceryl monostearate	1.00			
Stearyl alcohol	1.00			
Carbomer 940 (Carbopol 980)	0.30			
Crospovidone CL-M	1.00			
Hydroxypropyl methylcellulose (HPMC-Methocel K100M)	0.15			
Xanthan gum	0.15			
Glycerin	8.00			
Sodium PCA	2.00			
Citric acid	0.38			
Sodium citrate tribasic dihydrate	0.59			
Hydrous benzoyl peroxide	6.00			
Sodium hydroxide 18% solution	0.30			
Purified water	to 100			
Propellant (AP-70)	8.00			
Results	T-0	T-2, 30°C	T-2, 25°C	T-6, 30°C
Shakability	2	1	1	2
Foam Quality	G	G	E	G
Foam Color	white	white	white	white
Foam Odor	no odor	v.f.odor	no odor	v.f.odor
Density (mg/ml)	0.038	0.032	0.035	0.038
pH diluted (1:5)	4.57	4.39	4.47	4.17
Collapse Time (sec)	>300	>300	>300/G	>300
Expansion Time (sec)	48	N/M*	N/M*	N/M*

N/M*-not measured

Procedure (BPO035):**Step 1: Preparation of Water Phase (B)**

- 1.1.Heat 50g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2.Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Add carbomer solution and mix until thoroughly wetted and evenly dispersed, no clumps are detected
- 1.3.Cool step 1.2 to 50°C and add Xanthan gum with vigorous mixing
- 1.4. Heat step 1.3 to 70°C

- 1.5. Heat 100g water to 70°C
- 1.6. Add crospovidone to step 1.5 and mix.
- 1.7. Add step 1.6 to step 1.4 and mix.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase to the water phase at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to RT and not more than 40°C.
- 3.4. Add glycerin and sodium PCA to the emulsion while mixing thoroughly.
- 3.5. Cool to RT and not more than 30°C.
- 3.6. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 18g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60 minutes until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion (from step 5) is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Part C – Formulation 042 (without mineral oil)

Ingredients	BPO-042			
Cyclomethicone	1.00			
PEG-40 Stearate	3.00			
Polysorbate 60	1.00			
Glyceryl monostearate	1.00			
Stearyl alcohol	1.00			
Carbomer 941 (Carbopol 981)	0.20			
Crospovidone CL-M	1.00			
Hydroxypropyl methylcellulose (HPMC-Methocel K100M)	0.25			
Xanthan gum	0.25			
Citric acid	0.38			
Sodium citrate tribasic dihydrate	0.59			
Hydrous benzoyl peroxide	6.00			
Sodium hydroxide 18% solution	0.20			
Purified water	to 100			
Propellant (AP-70)	8.00			
Results	T-0	T-2, 30°C	T-2, 25°C	T-6, 30°C
Shakability	2	1	1	1
Foam Quality	E	G	E	G
Foam Color	white	white	white	white
Foam Odor	no odor	v.f.odor	no odor	strong
Density (mg/ml)	0.04	0.03	0.04	0.04
pH diluted (1:5)	4.55	4.39	4.52	4.10
Collapse Time (sec)	>300	>300	>300/G	>300
Expansion Time (sec)	68.00	N/M*	N/M*	N/M*

N/M*-not measured

Procedure (BPO042):

Step 1: Preparation of BPO paste (B)

- 1.1. Heat 50g water to 90°C, Add Methocel K100M with vigorous agitation until thoroughly wetted and evenly dispersed, no clumps are detected. Cool to 10 to 15°C while mixing until homogeneous and no particles are observed.
- 1.2. Add 4g crospovidone to 10g water and mix.
- 1.3. Add step 1.2 to step 1.1 and mix vigorously.

- 1.4. Start homogenization step 1.3 while cooling with ice bath. Add 31.76g Benzoyl peroxide and keep homogenization for 60 minutes.

Step 2: Preparation of Water Phase (A)

- 2.1. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Add 118g water to carbomer solution and heat to 50°C while mixing vigorously.
- 2.2. Add Xanthan gum with vigorous mixing.
- 2.3. Heat step 2.2 to 70°C

Step 3: Preparation of Oil Phase (A)

- 3.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 4: Emulsification

- 4.1. Add 0.6g sodium hydroxide to 10g purified water and mix
- 4.2. Add the oil phase (step 3) to the water phase (step 2) at 65 - 70°C with agitation.
- 4.3. Add step 4.1 to step 4.2 and continue agitation until PFF uniformity is reached.
- 4.4. Cool the emulsion to RT and not more than 30°C.
- 4.5. Check pH.
- 4.6. add water if necessary to obtain the correct weight.

Step 5: BPO Paste Addition

- 5.1. Add 72.57g of step 1.4 to the PFF (step 4) and mix for 30 min while cooling with ice bath. Check pH.
- 5.2. Add Citric acid and sodium citrate tribasic dihydrate to 15g water and mix.
- 5.3. Add step 5.2 to step 5.1 and mix.
- 5.4. Check pH, If pH higher than 4.5, add citric acid while mixing to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

Part D – Formulation 047 (with mineral oil)

Ingredients	BPO-047			
Mineral oil	6.00			
Cyclomethicone	1.00			
PEG-40 Stearate	3.00			
Polysorbate 60	1.00			
Glyceryl monostearate	1.00			
Stearyl alcohol	1.00			
Carbomer 941 (Carbopol 981)	0.30			
Hydroxypropyl methylcellulose (HPMC-Methocel K100M)	0.20			
Xanthan gum	0.20			
Glycerin	8.00			
Sodium PCA	2.00			
Citric acid	0.38			
Sodium citrate tribasic dihydrate	0.59			
Hydrous benzoyl peroxide	6.00			
Sodium hydroxide 18% solution	0.30			
Purified water	to 100			
Propellant (AP-70)	8.00			
Results	T-0	T-2, 30°C	T-2, 25°C	T-6, 30°C
Shakability	2	2	2	1
Foam Quality	E	G	G	E
Foam Color	white	white	white	white
Foam Odor	no odor	no odor	no odor	strong
Density (mg/ml)	0.04	0.03	0.04	0.04
pH diluted (1:5)	4.56	4.42	4.52	4.17
Collapse Time (sec)	>300	>300	>300/G	>300
Expansion Time (sec)	68.00	N/M*	N/M*	N/M*

N/M*-not measured

Note the Procedure for BPO047 is described in example 18

Part E – Formulation 048 (without mineral oil)

Ingredients	BPO-048
Cyclomethicone	1.00
PEG-40 Stearate	3.00
Polysorbate 60	1.00
Glyceryl monostearate	1.00
Stearyl alcohol	1.00

Ingredients	BPO-048			
Carbomer 940 (Carbopol 980)	0.30			
Crospovidone CL-M	1.00			
Hydroxypropyl methylcellulose (HPMC-Methocel K100M)	0.20			
Xanthan gum	0.20			
Glycerin	8.00			
Sodium PCA	2.00			
Citric acid	0.38			
Sodium citrate tribasic dihydrate	0.59			
Hydrous benzoyl peroxide	6.00			
Sodium hydroxide 18% solution	0.30			
Purified water	to 100			
Propellant (AP-70)	8.00			
Results	T-0	T-2, 30°C	T-2, 25°C	T-6, 30°C
Shakability	2	1	1	1
Foam Quality	G+	G	G	G
Foam Color	white	white	white	white
Foam Odor	no odor	v.f.odor	no odor	strong
Density (mg/ml)	0.039	0.033	0.035	0.039
pH diluted (1:5)	4.58	4.46	4.57	4.19
Collapse Time (sec)	>300	>300	>300/G	>300
Expansion Time (sec)	57	-	-	-

Procedure (BPO048):

Step 1: Preparation of Water Phase (B)

- 1.1. Heat 200g water to 70°C, add methocel with vigorous mixing until thoroughly wetted and evenly dispersed, no clumps are detected.
- 1.2. Add carbomer to water while mixing to dissolution and add base ("Carbomer solution"). Add carbomer solution and mix until thoroughly wetted and evenly dispersed, no clumps are detected
- 1.3. Cool step 1.2 to 50°C and add Xanthan gum with vigorous mixing
- 1.4. Heat step 1.3 to 70°C
- 1.5. Heat 150g water to 70°C
- 1.6. Add crospovidone to step 1.5 and mix.
- 1.7. Add step 1.6 to step 1.4 and mix.

Step 2: Preparation of Oil Phase (A)

- 2.1. Heat all ingredients of the oil phase to 70°C until complete melting and homogeneity is obtained.

Step 3: Emulsification

- 3.1. Add the oil phase (step 2) to the water phase (step 1) at 65 - 70°C with agitation
- 3.2. Agitation continues until PFF uniformity is reached.
- 3.3. Cool the emulsion to RT and not more than 40°C.
- 3.4. Add glycerin and sodium PCA to the emulsion while mixing thoroughly.
- 3.5. Cool to RT and not more than 30°C.
- 3.6. Check pH.

Step 4: Buffer addition

- 4.1. Add Citric acid and sodium citrate tribasic dihydrate to 58g water and mix.
- 4.2. Add step 4.1 to step 3 and mix.
- 4.3. Check pH.
- 4.4. Check the final weight of emulsion and add water if necessary to obtain the correct weight.

Step 5: Homogenization and Benzoyl Peroxide addition

- 5.1. Start homogenization step 4 while cooling with ice bath. Add Benzoyl peroxide and keep homogenization for 60-90 minutes until uniformity and no agglomeration is seen in microscopic observation.

Step 6: pH adjustment

- 6.1. Verify temperature emulsion (from step 5) is less than 30°C. Check pH, to obtain a pH of 4.5±0.2.

Step 7: Canisters Filling and Crimping

Fill canister with PFF and crimped with valves

Step 8: Pressurizing

Canisters are filled with 8% propellant.

[0330] Comments: 6-month physical stability at 25⁰ and at 30⁰C can be seen for each of the different examples of the two types of formulations that have been developed emollient (+6% oil) and mineral oil-free.

Example 24 – Viscosity and physical parameters study

This example describes measurements with 8% pentane (to simulate viscosity of formulation in canister with propellant) and without 8% pentane for various formulations including a prior art formulation.

Part A - Physical Results

Formula name (test material type, closure system)	Viscosity of PFF (cPs)	Viscosity PFF +8% pentane (cPs)	Viscosity ratio (%) (cPs)	Foam quality	Density	Bubble size (µm)	Collapse Time To
BPO-032(see Example 23)	7454	7214 7086	96.78% 95.06%	E	0.034	74	>300
BPO-035 (see Example 23)	5103	1462	28.64	G	0.038	86	>300
BPO-042 (see Example 23)	5551	2615	47.12	E	0.040	63	>300
BPO-047-6(see Example 23)	5855	4463	76.23	E	0.039	99	>300
BPO-048 (see Example 23)	5471	2516	46.00	G+	0.039	76	>300
BPO-047(1%) (see Example 18)	1280	885	69.14	E	N/M	N/M	N/M
BPO-047 (15%) (see Example 18)	6559	6495	99.02	E	N/M	N/M	N/M
BPO-049 (Example 3 US 2007/0003585)	1045377	930601	89.02	N/R	N/M	N/M	
BPO-035 (0.85% Carbopol 980) (See Part B)	16764	9870	58.87	E	N/M	N/M	N/M
BPO-035 (only 0.30% Carbopol 980) (See Part B)	484	63	0.13	G+	N/M	67	N/M
BPO-051 (only 0.30% pemulen TR-2) (See Part B)	895	797	89.05	G	N/M	122	N/M
BPO-050 (only 0.30% xanthan gum)(See Part B)	879	802	91.24	G-	N/M	149	N/M

N/MNot Measured; Note:The formulations are set out below in Part D below.

[0331] Comments: The pre-foam formulation viscosities are low for formulations with carbopol. Addition of simulated propellant results in some

reduction of viscosity except where the concentration of BPO is very high (15%). The ratio (blue) varies from about 25% to 75% with one or two exceptions. The unexpected little or no change in viscosity on adding pentane may be a reflection of lack of solubility of pentane in the formulation. When the level of carbopol was increased nearly threefold from 0.3 to 0.85% the viscosity of the pre foam formulation on average approximately tripled. When the formulation Example 3 of US 2007/0003585 was prepared the viscosity was found to be in excess of 1 million cps. A comparison of low levels of carbopol, pemulen and xanthan disclosed that whilst all produced good quality foam the foam appearance using carbopol alone and likewise bubble size was slightly better than pemulen which in turn was slightly better than xanthan.

Part B

Polymer test -Visual Inspection (pressurized glass bottle)

a) Benzoyl Peroxide:

	T-0	6M
BPO-032-080330*	Homogenous	Homogenous
BPO-035-080331	Homogenous	Homogenous
BPO-042-080401	Homogenous	Homogenous
BPO-047-080402	Homogenous	Homogenous
BPO-048-080403	Homogenous	Homogenous

b) Formulation:

	T-0	6M
BPO-032-080330*	Homogenous	Creaming 90/10-reversible.
BPO-035-080331	Homogenous	Creaming 90/10-reversible.
BPO-042-080401	Homogenous	Creaming 85/15-reversible.
BPO-047-080402	Homogenous	Creaming 90/10-reversible.
BPO-048-080403	Homogenous	Creaming 80/20-reversible

Note in the marks cases *- BPO-032 was tested just to 3 month.

[0332] Comments: although the formulations showed a small amount of creaming which was reversible after six months the BPO remained homogenous and caking and sedimentation were not observed.

Part C

[0333] Physical results (including Foam Quality) appear in example 24. See the photograph in Figure 12. All three bottles represent formulation BPO035, but only with one polymer. In bottle #1 the polymer is Carbopol 980, 0.3% w/w. In bottle #2 the polymer is xanthan gum, 0.3% w/w. In bottle #1 the polymer is pemulen TR-2, 0.3% w/w.

PART D FORMULATIONS from Part ANote**BPO-035-081123 (0.85% Carbopol 980)**

Ingredient name	%w/w
Mineral oil	6.00
Cyclomethicone	1.00
PEG-40 Stearate	3.00
Polysorbate 60	1.00
Glyceryl monostearate	1.00
Stearyl alcohol	1.00
Hydroxypropyl methylcellulose	0.15
Xanthan gum	0.15
Purified water	65.67
Crospovidone	1.00
Carbopol 980	0.85
NaOH 18% solution	0.49
Citric acid	0.31
Sodium citrate tribasic dihydrate	0.44
Glycerin	8.00
Sodium PCA	2.00
Benzoyl Peroxide	7.94
Control:	100.00
Propellant	8.00

BPO-035-081124 (0.30% Carbopol 980)

Ingredient name	%w/w
Mineral oil	6.00
Cyclomethicone	1.00
PEG-40 Stearate	3.00
Polysorbate 60	1.00
Glyceryl monostearate	1.00
Stearyl alcohol	1.00
Purified water	67.84
Carbopol 980	0.30
NaOH 18% solution	0.17
Citric acid	0.31
Sodium citrate tribasic dihydrate	0.44
Glycerin	8.00
Sodium PCA	2.00
Benzoyl Peroxide	7.94
Control:	100.00
Propellant	8.00

BPO-051-081124 (0.30% Pemulen TR-2)

Ingredient name	%w/w
Mineral oil	6.00
Cyclomethicone	1.00
PEG-40 Stearate	3.00
Polysorbate 60	1.00
Glyceryl monostearate	1.00
Stearyl alcohol	1.00
Purified water	67.84
PemulenTR-2	0.30
NaOH 18% solution	0.17
Citric acid	0.31
Sodium citrate tribasic dihydrate	0.44
Glycerin	8.00
Sodium PCA	2.00
Benzoyl Peroxide	7.94
Control:	100.00
Propellant	8.00

BPO-050-081124 (0.30% Xanthan Gum)

Ingredient name	%w/w
Mineral oil	6.00
Cyclomethicone	1.00
PEG-40 Stearate	3.00
Polysorbate 60	1.00
Glyceryl monostearate	1.00
Stearyl alcohol	1.00
Purified water	68.01
Xanthan gum	0.30
Citric acid	0.31
Sodium citrate tribasic dihydrate	0.44
Glycerin	8.00
Sodium PCA	2.00
Benzoyl Peroxide	7.94
Control:	100.00
Propellant	8.00

BPO-049-081123 (Stiefel Patent Application-Example 3)

Ingredient name	%w/w
Water purified	89.42
Benzoyl peroxide hydrous	2.84
Clyndamycin phosphate	1.28
Tretinoin	0.102
Glycerin	4.99
Carbopol 980	0.84
Sodium hydroxide (18% sol.)*	0.49
Methyl paraben	0.04
Total	100.00

Example 25 -Propellant studies

[0334] In an initial study AP 70 was found to be preferred over AP 46. **A visual foam quality comparison test between AP-70 and AP-46 was performed using BPO 014., The foam quality observed with AP-70 was slightly better.**

[0335] In a further study formulation BPO042 was chosen as a representative example in which to examine the effects of different propellants.

[0336] As shown in Figure 13, 3 glass bottles were filled with 20 gr. PFF and 8% (1.6gr.) different propellants: AP-70, AP-46 and Propane. All bottles were filled on November 23, 2008. Photo was taken on November 24, 2008

Comments:

As clearly demonstrates, after 24 hours at RT, all types of propellants showed similar behavior- stable and homogenous

Example 26a –Citrate Buffer studies

[0337] Procedure: 0.3g Carbopol 980 was added to 67.84 g water with vigorous mixing until thoroughly wetted and evenly dispersed with no clumps

detected. then, 0.17g NaOH 18% solution was added (part of water phase BPO035). This combination produced the gel demonstrated in photographs #1 & 2 of Figure 14. The final pH was 4.36. Then, Buffer was added (0.31g citric acid and 0.44 g Sodium citrate) and the viscosity decreased dramatically, as demonstrated in photograph #3 of Figure 14. The final pH was 4.13. Thus whilst the final pH of both the gel with NaOH and the liquid solution with the addition of citrate buffer was substantially identical the viscosity was radically and visually different. In the case of the whole emulsion formulation (BPO035) and the case of just the water phase of BPO035, the buffer was added at low temperature (25-30°C).

[0338] Comments: Citrate buffer surprisingly destroys gel structure and significantly reduces formulation viscosity. Thus using citrate buffer with carbopol provides a significant advantage in that whilst viscosity appears low the polymer is unexpectedly able to hold the BPO suspension stable. Carbopol has a similar viscosity from pH=4 and way above, so these results are surprising.

Example 26b –Lactate Buffer studies

Procedure: 0.3gr. Carbopol 980 was added to 67.84 gr. water with vigorous mixing until thoroughly wetted and evenly dispersed with no clumps detected. then, 0.19gr. NaOH 18% solution were added (part of water phase BPO035). This combination produced the gel demonstrated as demonstrate in “Citrate Buffer studies” The final pH was 4.75. Then, lactic acid (0.50gr.) first and then afterwards ammonium lactate (about 11gr) were added for final pH 4.50. It was observed that the viscosity also decreased dramatically, upon addition of the acid and the formulation became fluid as demonstrated in FIG 14 photograph #3 in “Citrate Buffer studies”. It remained fluid after addition of ammonium lactate.

What is claimed is:

1. A foamable composition for treating acne comprising:
 - a) a prefoam emulsion composition comprising:
 - i. benzoyl peroxide;
 - ii. one or more surface-active agents;
 - iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; and
 - iv. water;
 - b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a viscosity of the prefoam composition of less than about 8000 centipoises (cps) at room temperature; and
 - c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature.
2. The composition of claim 1, wherein the foam produced from the foamable composition has an average bubble size of less than about 150 microns.
3. The composition of claim 1, wherein the prefoam emulsion composition further comprises a pH adjusting component selected from the group consisting of, a base or a buffer system, said pH adjusting component selected to be able to gel the polymeric additive..
4. The composition of claim 3, wherein the pH of the prefoam emulsion composition is between about 4.0 and about 6.0.
5. The composition of claim 4, wherein the buffer system is at a pH less than the pH of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion.
6. The composition of claim 1, wherein the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.

7. The composition of claim 1, further comprising about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA).
8. The composition of claim 1, further comprising about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.
9. The composition of claim 8, wherein the moisturizing complex has at least three of the following characteristics:
 - a) improves the chemical stability of BPO in the composition;
 - b) improves the homogeneity of BPO in the composition;
 - c) improves the quality of the foam produced from the foamable propellant composition;
 - d) improves the hydration of skin after 7 hours by at least about 20%.
10. The composition of claim 1, further comprising about 1% glycerol stearate and one of about 1% stearyl alcohol or about 1% cetostearyl alcohol.
11. The composition of claim 1, wherein the polymeric additive comprises an amphiphilic polymer,
12. The composition of claim 11, wherein the amphiphilic polymeric additive comprises a carbomer.
13. The composition of claim 1, wherein the concentration range of benzoyl peroxide is selected from the group of (i) between about 0.005% and about 0.5%; (ii) between about 0.5% and about 2%; (iii) between about 2% and about 5%; (iv) between about 5% and about 10%; and (v) between about 10% and about 15%.
14. The composition of claim 1, wherein the concentration of the one or more surface-active agents is between about 0.1% and about 5%.

15. The composition of claim 1, wherein the surface-active agent is selected from the group consisting of Steareth-21, Steareth-2, steareth 20, Polysorbate 80, Polysorbate 60, Polysorbate 20, ceteth 20, PEG 40-stearate, PEG 100-stearate, PEG-30 dipolyhydroxystearate, sorbitan stearate (span 60), sorbitan palmitate (span 40), sorbitan laurate (span 20), sorbitan monooleate (span 80), glycerol monostearate, glyceryl stearate, laureth 4, cetareth 20, macrogol cetostearyl ether, ceteth 2 (Lipocol C-2), sucrose distearate (Sisterna SP30), polyoxyethylene (100) stearate, and mixtures thereof.
16. The composition of claim 11, wherein the polymeric additive further comprises a polymeric agent selected from the group consisting of methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (Methocel), hydroxyethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose, Sodium CMC, carboxymethylhydroxyethylcellulose, xanthan gum, guar gum, carrageenin gum, locust bean gum and tragacanth gum and mixtures of two or more thereof.
17. The composition of claim 7, further comprising about 1% to about 15% by weight of an oil.
18. The composition of claim 1, further comprising about 1% to about 15% by weight of an oil, wherein the oil is selected from the group consisting of mineral oil, silicone oil, jojoba oil, MCT oil and mixtures of two or more thereof.
19. The composition of claim 1, further comprising about 0.1% to about 5% by weight of a therapeutically active foam adjuvant selected from the group consisting of fatty alcohols having 15 or more carbons in their carbon chain; fatty acids having 16 or more carbons in their carbon chain; fatty alcohols derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; fatty alcohols having at least one double bond; fatty acids having at least one double

bond; branched fatty alcohols; branched fatty acids; fatty acids substituted with a hydroxyl group; cetyl alcohol; stearyl alcohol; arachidyl alcohol; behenyl alcohol; 1-triacontanol; hexadecanoic acid; stearic acid; arachidic acid; behenic acid; octacosanoic acid; 12-hydroxy stearic acid and mixtures thereof.

20. The composition of claim 1, further comprising at least one additional therapeutic agent, which is an antibiotic agent, selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, lincomycin class, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof, and naturally occurring antibiotic compounds.
21. The composition of claim 20, wherein the antibiotic is clindamycin.
22. A foamable composition for treating acne comprising:
 - a) a prefoam emulsion composition comprising:
 - i. benzoyl peroxide;
 - ii. one or more surface-active agents;
 - iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive;
 - iv. about 5% to about 15% by weight of the total composition of a moisturizing complex; and
 - v. water;
 - b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a prefoam composition that is fluid at room temperature; and
 - c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition,

wherein the foamable propellant composition is fluid at room temperature.

23. The composition of claim 22, wherein the foam produced from the foamable propellant composition has an average bubble size of less than about 150 microns.
24. The composition of claim 22, wherein the prefoam emulsion composition further comprises a pH adjusting component selected from the group consisting of a base or a buffer system, said pH adjusting component selected to be able to gel the polymeric additive..
25. The composition of claim 24, wherein the pH of the prefoam emulsion composition is between about 4.0 and about 6.0.
26. The composition of claim 25, wherein the buffer system is at a pH less than the pH of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion.
27. A method of treating acne, the method comprising administering topically to a subject having acne a foamable composition of any one of claims 1-26.
28. A foamable composition comprising:
 - a) a prefoam composition comprising:
 - i. a suspended solid active agent;
 - ii. one or more surface-active agents;
 - iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive;
 - iv. up to about 2% by weight of the total composition of a buffer system; and
 - v. water,wherein the viscosity of the prefoam composition is less than about 8000 centipoises (cps) at room temperature; and
 - b) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition,

wherein the viscosity of the foamable composition is less than about 8000 centipoises (cps) at room temperature.

29. A foamable composition comprising:
- a) a prefoam composition comprising:
 - i. a suspended solid active agent;
 - ii. one or more surface-active agents;
 - iii. about 0.001% to about 1% by weight of the total composition of at least one polymeric additive;
 - iv. about 5% to about 15% by weight of the total composition of a moisturizing complex; and
 - v. water;
 - b) up to about 2% by weight of the total composition of a buffer system, wherein the buffer system is selected to provide a prefoam composition that is fluid at room temperature; and
 - c) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition, wherein the foamable propellant composition is fluid at room temperature.
30. The composition of claim 29, wherein the foam produced from the foamable propellant composition has an average bubble size of less than about 150 microns.
31. The composition of claim 29, wherein the suspended solid agent has an average particle size of less than about 35 microns.
32. The composition of claim 29, wherein the buffer system comprises citric acid and sodium citrate or lactic acid and ammonium lactate.
33. The composition of claim 29, further comprising about 5% to about 15% a moisturizing complex comprising glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA).
34. The composition of claim 29, further comprising about 5% to about 30% of a moisturizing complex comprising an oil and at least one of glycerine and

a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.

35. The composition of claim 1, further comprising at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an organic polar solvent, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.
36. The composition of claim 35, wherein the at least one organic carrier is present in an amount selected from the group consisting of (i) about 2% to about 5%; (ii) about 5% to about 10%; (iii) about 10% to about 20%; and (iv) about 20% to about 50% by weight.
37. The composition of claim 1, further comprising a penetration enhancer.
38. The composition of claim 37, wherein the penetration enhancer is selected from the group consisting of propylene glycol, butylene glycols, hexylene glycol, glycerol, pentaerythritol, sorbitol, mannitol, oligosaccharides, dimethyl isosorbide, monooleate of ethoxylated glycerides having about 8 to 10 ethylene oxide units, polyethylene glycol 200-600, transcutol, glycofurol and cyclodextrins.
39. The composition of claim 1, wherein the foamable composition further comprises at least one additional therapeutic agent selected from the group consisting of an a steroidal anti-inflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an androgen, an estrogen, a prostaglandin, an antiandrogen agent, a testosterone inhibitor, a dihydrotestosterone inhibitor, an antifungal agent, an antiviral agent, an antiparasitic agent, a retinoid, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, a keratolytic agent, urea, a urea derivative, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a

haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebacic acid, adipic acid, fumaric acid, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, benzoyl chloride, calcium hypochlorite, magnesium hypochlorite, an anti-wrinkle agent, a radical scavenger, a metal, silver, a metal oxide, titanium dioxide, zinc oxide, zirconium oxide, iron oxide, silicone oxide, an organo-metallic compound, and organo-boron compound, an organo-berrilium compound, talc, carbon, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

40. The composition of claim 39, wherein the additional therapeutic agent is sensitive to oxidation and wherein the composition includes a stabilizing agent which acts as an effective barrier to the possible degradedative interaction of the peroxide and the additional therapeutic agent.
41. The composition of claim 15, wherein the surface active agent comprises about 0.1% to about 5% by weight of a mixture of Glyceryl monostearate and PEG-40 Stearate.
42. The composition of claim 1, further comprising about 1% to about 25% by weight of a polar solvent.
43. The foamable composition of claim 42, wherein the polar solvent is selected from polyols, glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, sulfoxides, dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, acetamide oleates, triolein; various alkanoic acids, caprylic acid; lactam

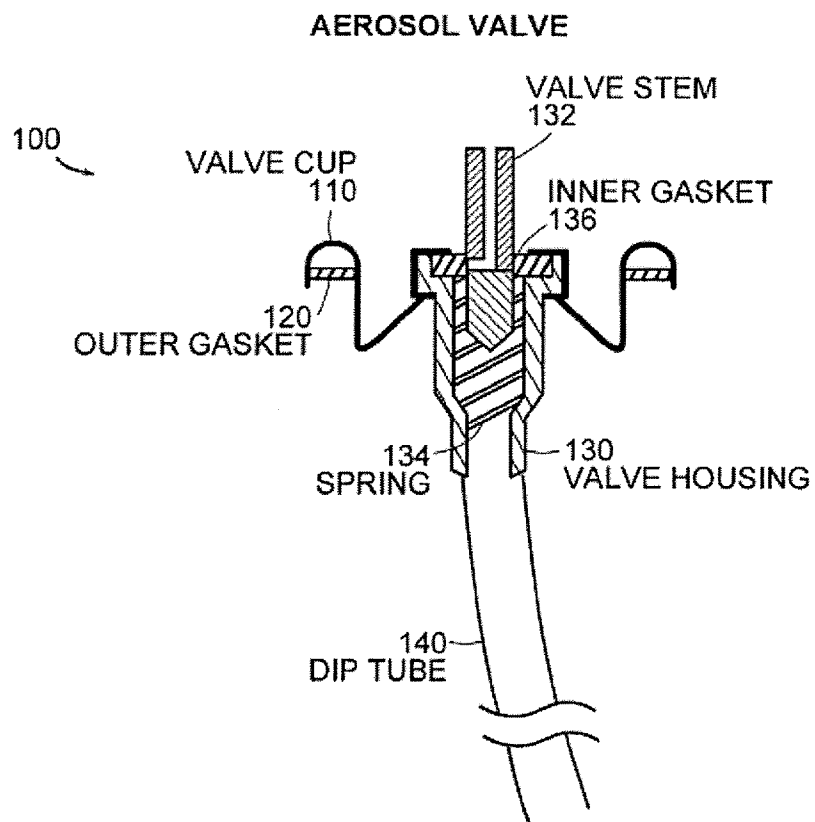
compounds, azone; alkanols, dialkylamino acetates, and admixtures thereof.

44. The foamable composition of claim 42, wherein the polar solvent is selected from polyethylene glycol (PEG), PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD), PEG 4000, PEG 6000, PEG 10000 and mixtures thereof.
45. A therapeutic kit to provide a safe and effective dosage for treating acne, including an aerosol packaging assembly comprising:
- a container accommodating a pressurized product; and
- an outlet capable of releasing the pressurized product as a foam;
- wherein the pressurized product comprises a foamable composition according to any one of claims 1-26.
46. The kit of claim 45, wherein upon release from the container, a shear-sensitive foam, having a density range selected from (1) between about 0.02 g/mL and about 0.1 g/mL; and (2) between about 0.02 g/mL and about 0.1 g/mL, is produced.
47. A therapeutic kit to provide a safe and effective dosage for treating acne, including an aerosol packaging assembly comprising:
- a. a first container accommodating a first pressurized product;
- b. a second container accommodating a second pressurized product and
- c. at least one outlet capable of releasing the first pressurized product and the second pressurized product as a foam;
- wherein the first pressurized product comprises a foamable composition according to claim 1, and the second pressurized product comprises a foamable composition containing one additional therapeutic agent.

48. The kit of claim 47, wherein the additional therapeutic agent is selected from antibiotics, retinoids, keratolytics and azelaic acid (AZA).
49. The kit of claim 47, wherein the additional therapeutic agent is an antibiotic selected from the group consisting of beta-lactam antibiotics, aminoglycosides, ansa-type antibiotics, anthraquinones, antibiotic azoles, antibiotic glycopeptides, macrolides, antibiotic nucleosides, antibiotic peptides, antibiotic polyenes, antibiotic polyethers, quinolones, antibiotic steroids, sulfonamides, tetracycline, dicarboxylic acids, antibiotic metals, oxidizing agents, substances that release free radicals and/or active oxygen, cationic antimicrobial agents, quaternary ammonium compounds, biguanides, triguanides, bisbiguanides and analogs and polymers thereof and naturally occurring antibiotic compounds.
50. The kit of claim 47, wherein the additional therapeutic agent is clindamycin.
51. A method of enhancing the stability of a foamable composition comprising benzoyl peroxide for treating acne, the method comprising adding a moisturizing complex to the foamable composition.
52. The method of claim 51, wherein the moisturizing complex comprises about 5% to about 15% by weight of the total composition.
53. The method of claim 51, wherein the moisturizing complex comprises glycerin and sodium PCA.
54. The method of claim 51, wherein the moisturizing complex includes an oil and comprises about 5% to about 30% by weight of the total composition and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.
55. A method of reducing the dryness, irritation, or both associated with the use of a foamable composition containing benzoyl peroxide for treating acne, the method comprising adding a moisturizing complex to the foamable composition.

56. The method of claim 55, wherein the moisturizing complex comprises about 5% to about 15% by weight of the total composition.
57. The method of claim 55, wherein the moisturizing complex comprises glycerin and sodium PCA.
58. The method of claim 55, wherein the moisturizing complex includes an oil and comprises about 5% to about 30% by weight of the total composition and at least one of glycerine and a salt of 2-pyrrolidone-5-carboxylic acid (PCA), wherein the oil comprises mineral oil and a silicone oil.
59. A method of making a foamable composition comprising containing a suspended solid active agent, comprising:
- a) forming a prefoam emulsion comprising a solid active agent, one or more surface-active agents; about 0.001% to about 1% by weight of the total composition of at least one polymeric additive; a pH adjusting component selected to be able to gel the polymeric additive; about 5% to about 15% by weight of the total composition of a moisturizing complex; and water, wherein the aqueous phase has a thickness sufficient to suspend the active agent;
 - b) adding a buffer system to the prefoam emulsion to reduce the viscosity of the prefoam formulation, said buffer system at a pH that is less than that of the prefoam emulsion before addition of the buffer and is selected to provide a liquid prefoam emulsion.; and
 - c) introduce a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition to the reduced viscosity prefoam emulsion to obtain a foamable composition having a stable suspended active solid and that is fluid at room temperature.
60. The method of claim 59, wherein the prefoam emulsion has a pH in the range for 4 to 6.
61. The method of claim 59, wherein the prefoam emulsion has a pH of less than about 5.

62. The method of claim 59, wherein the foam produced from the foamable composition has an average bubble size of less than about 150 microns.

**Figure 1**

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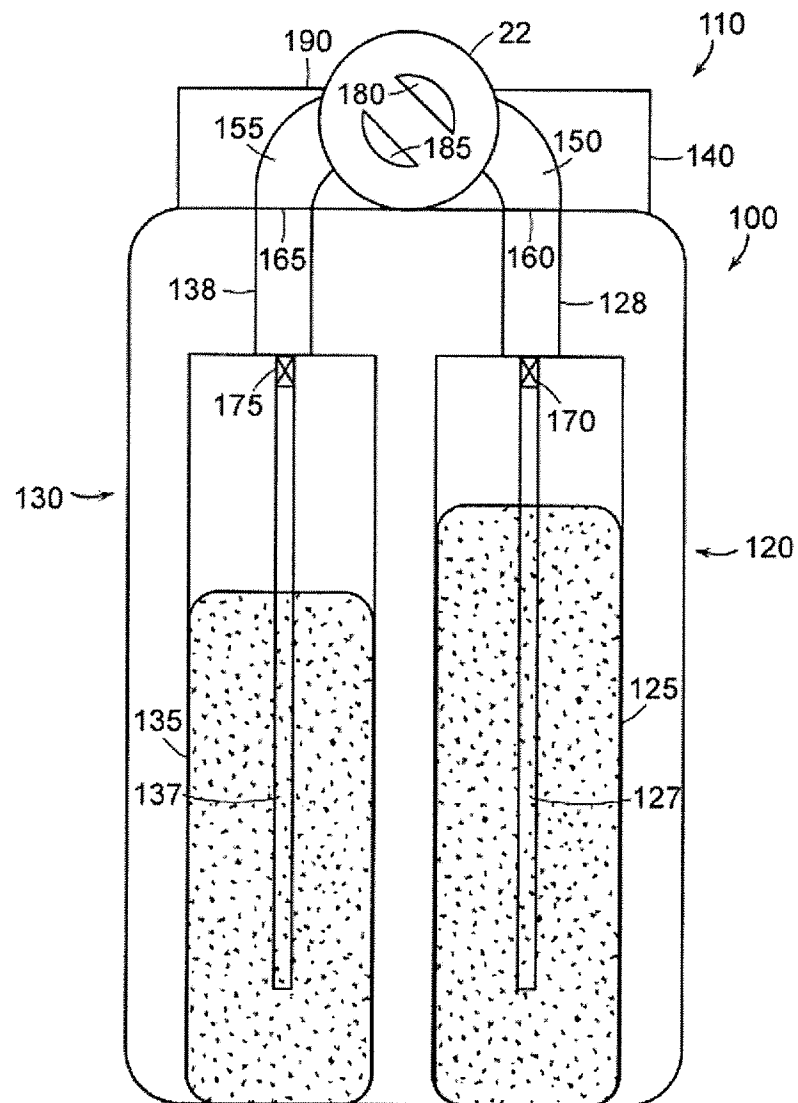


Figure 2

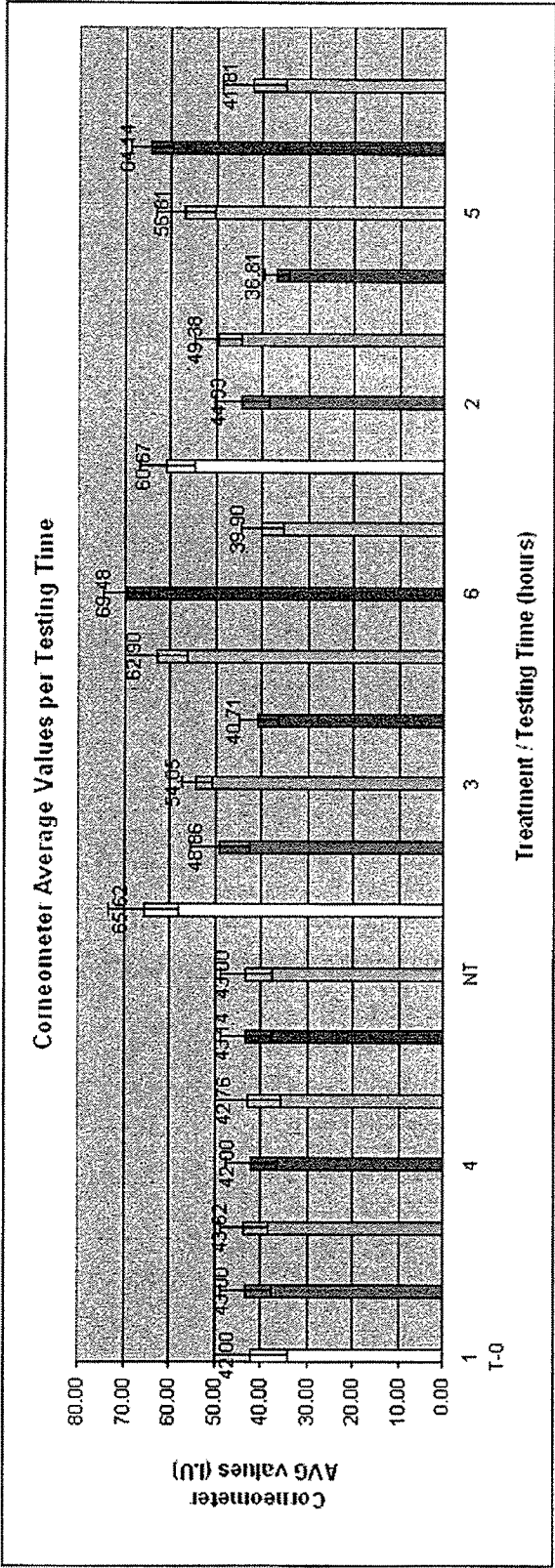


Figure 3

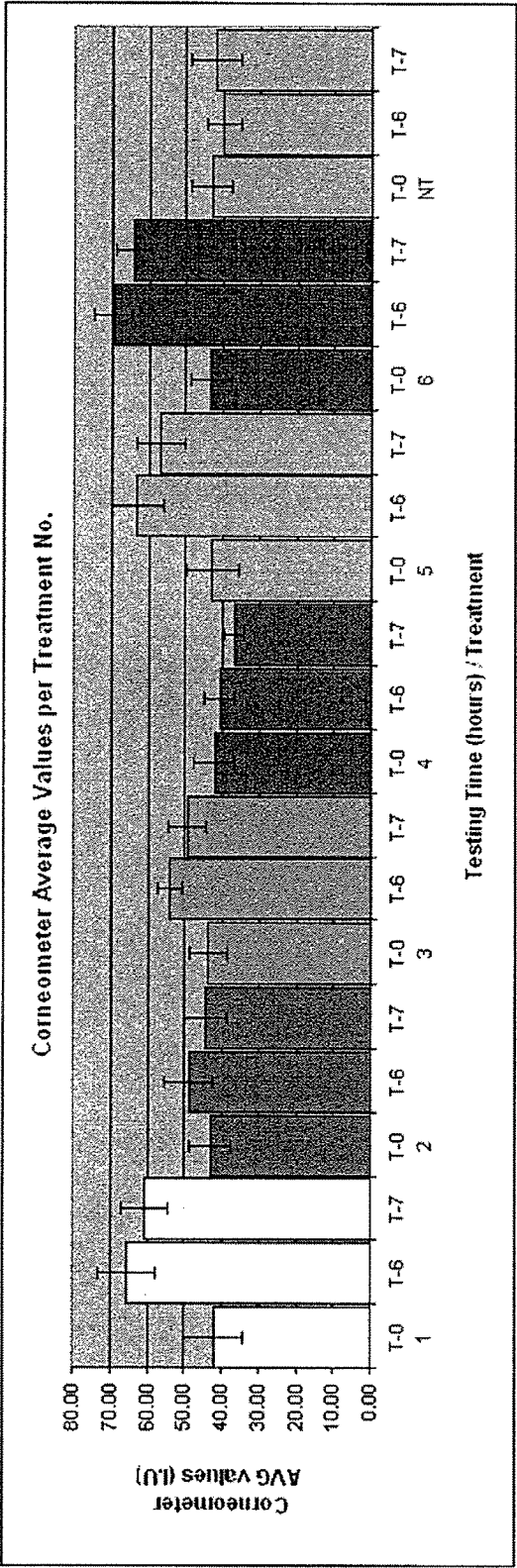


Figure 4

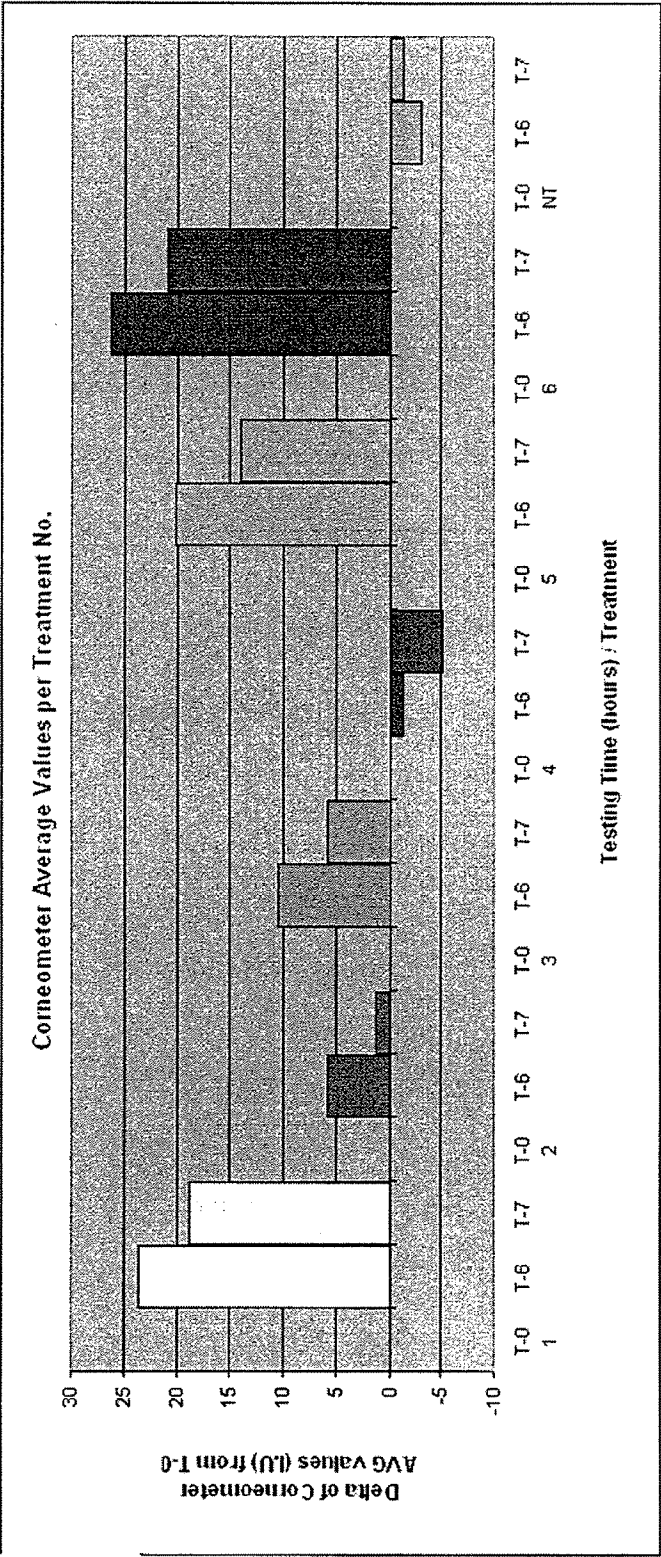
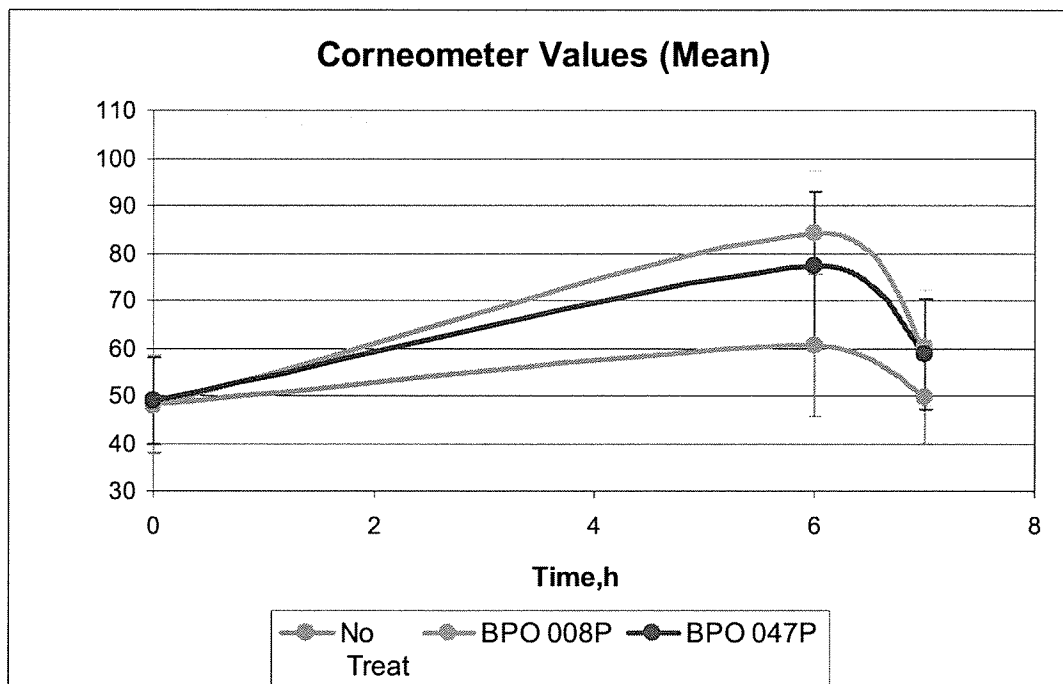
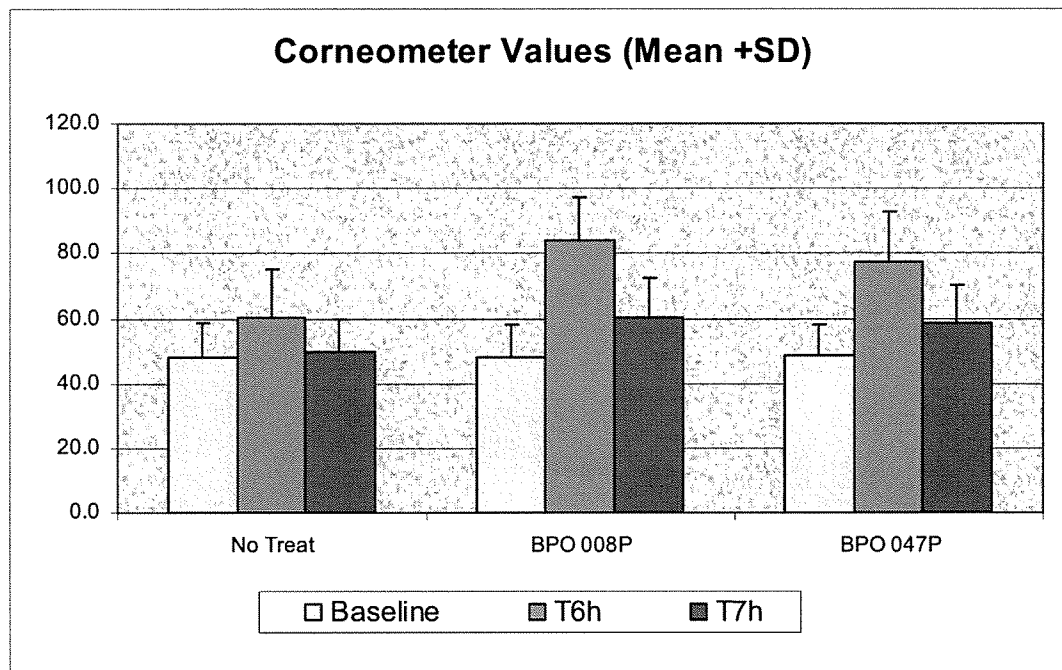


Figure 5

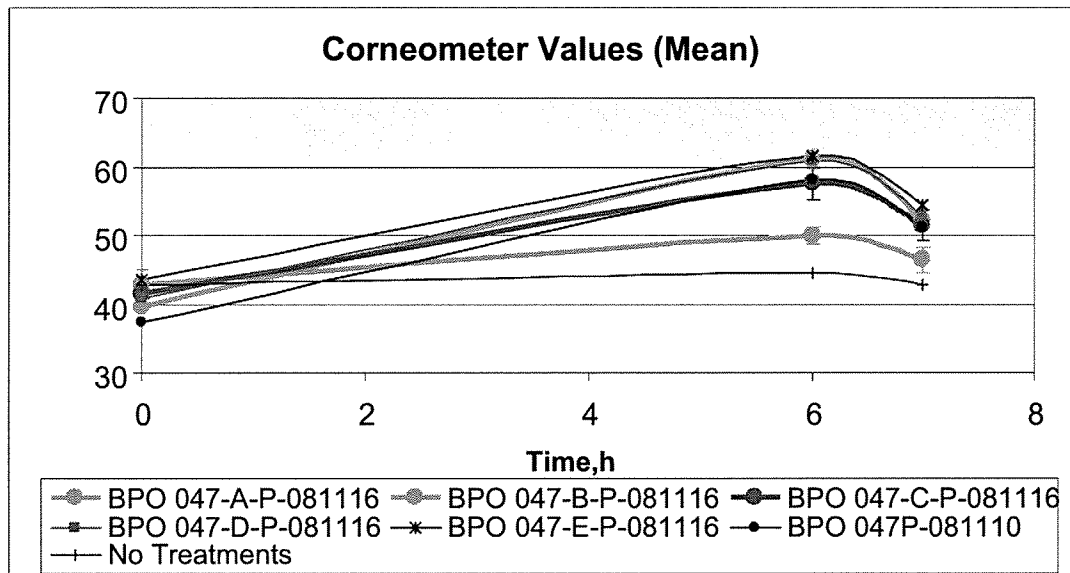
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**Figure 6**

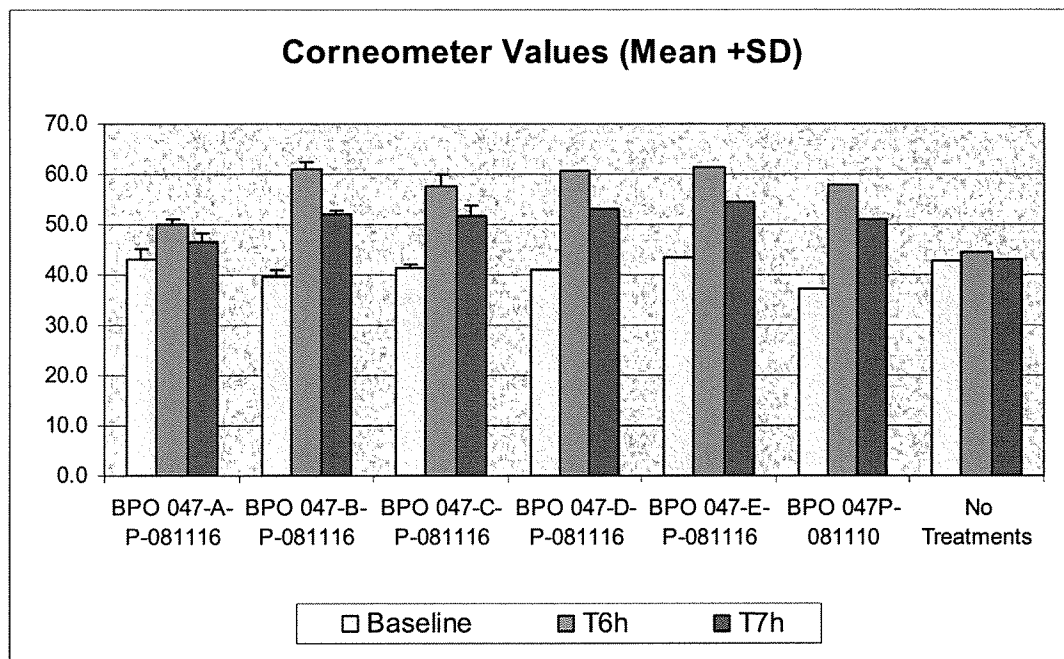
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**Figure 7**

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**Figure 8**

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**Figure 9**

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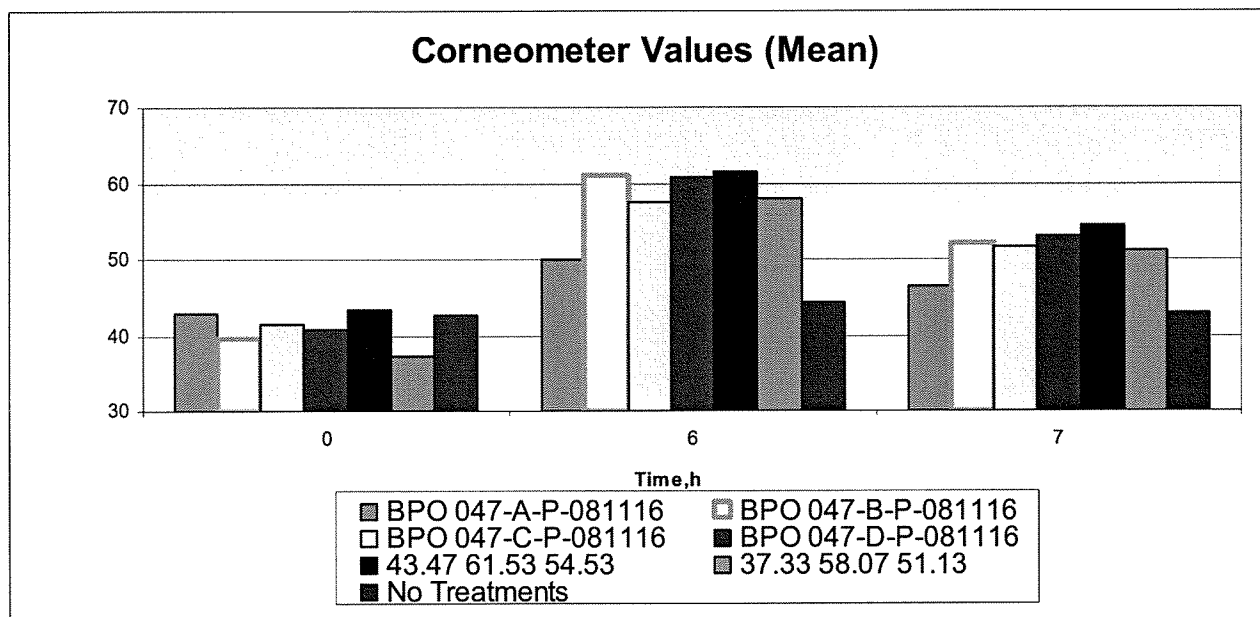
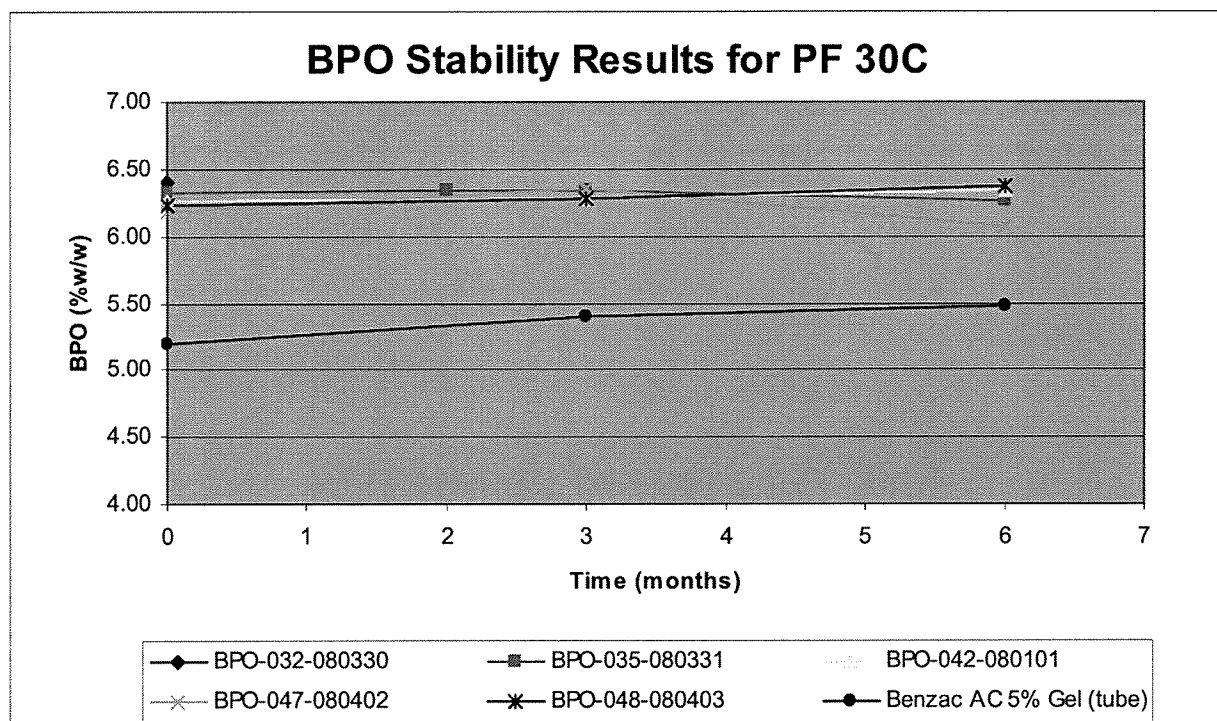


Figure 10

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**Figure 11**

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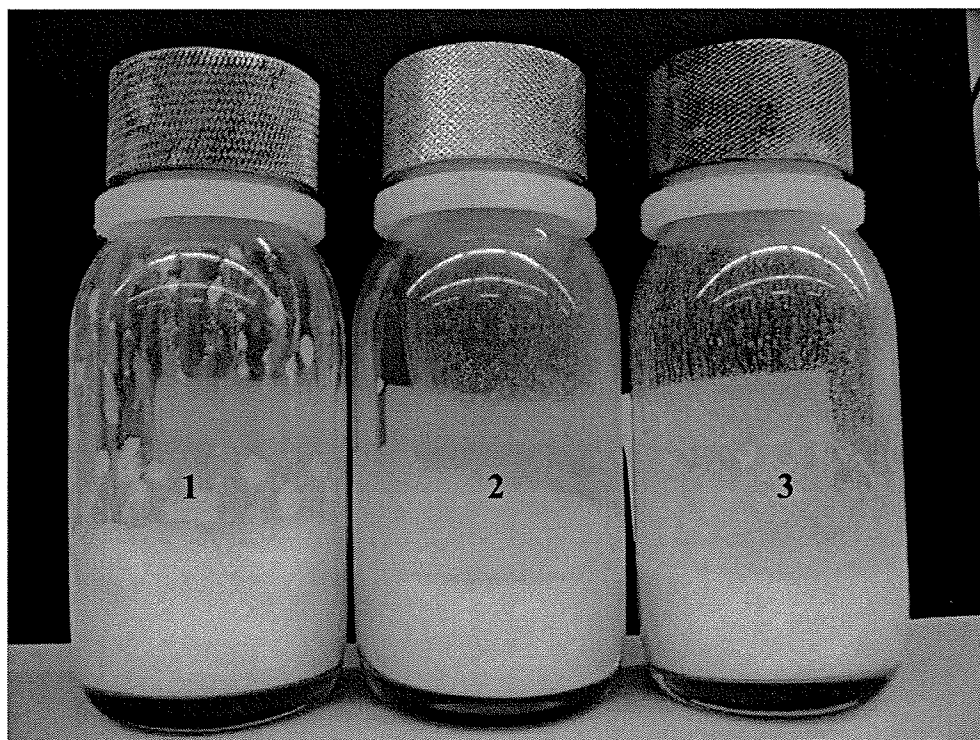


Figure 12

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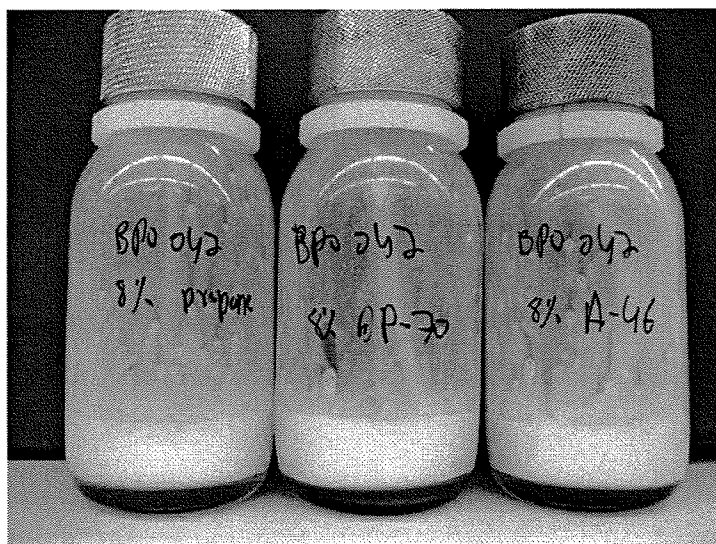


Figure 13

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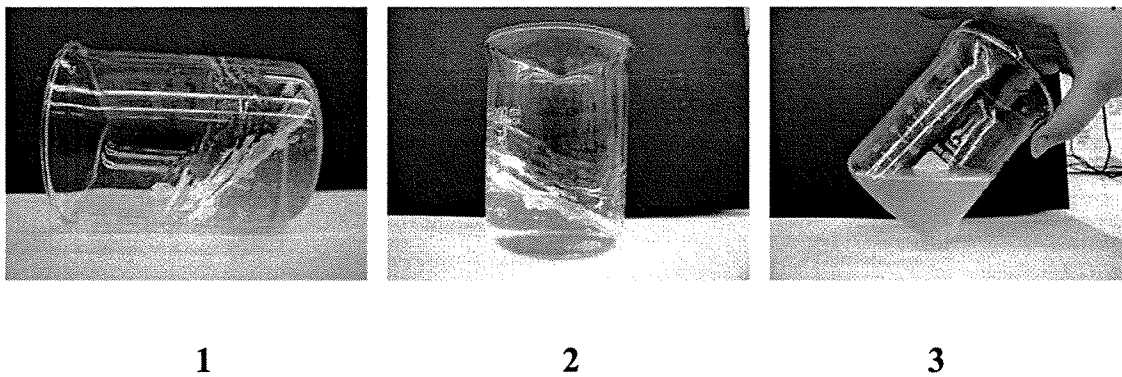


Figure 14

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Figure 15