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(54) **FOAMABLE VEHICLE AND  
PHARMACEUTICAL COMPOSITIONS  
THEREOF**

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(57) **ABSTRACT**

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**Related U.S. Application Data**

(63) Continuation of application No. 12/767,511, filed on Apr. 26, 2010, now Pat. No. 8,362,091, which is a continuation of application No. 11/430,599, filed on May 9, 2006, now Pat. No. 7,704,518, which is a continuation-in-part of application No. 10/835,505, filed on Apr. 28, 2004, now Pat. No. 7,820,145.

A hygroscopic pharmaceutical composition includes at least one hygroscopic substance at a concentration sufficient to provide an *A<sub>w</sub>* value of at least 0.9 and an antiinfective agent. A foamble pharmaceutical carrier includes about 50% to about 98% of a polar solvent selected from the group consisting of a polyol and PEG; 0% to about 48% of a secondary polar solvent; about 0.2% to about 5% by weight of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent; and a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**Candida albicans**

Composition A effective

Compositions B and C ineffective

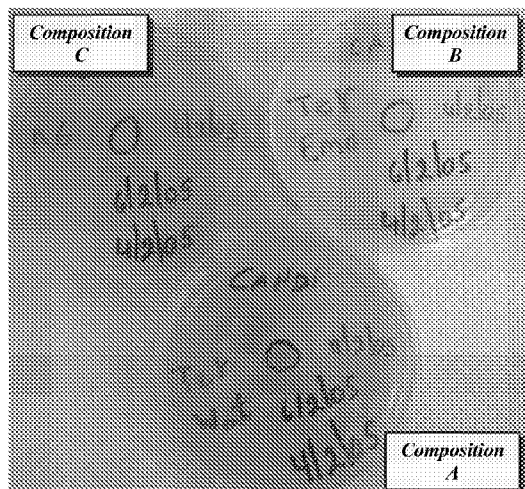


Fig. 1A

**Trichophyton rubrum**

Compositions A, B and C effective

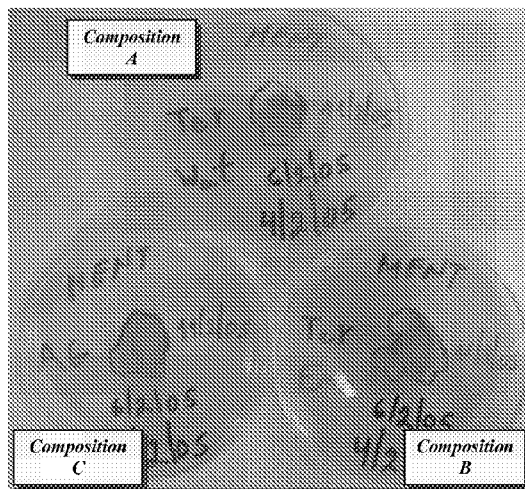


Fig. 1B

**Trichophyton mentagrophytes**

Compositions A and B effective

Composition C ineffective

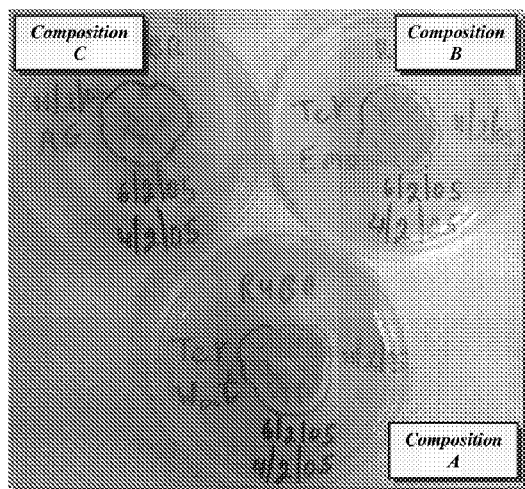


Fig. 1C

**Microsporum canis**

Composition A and B effective

Composition C ineffective

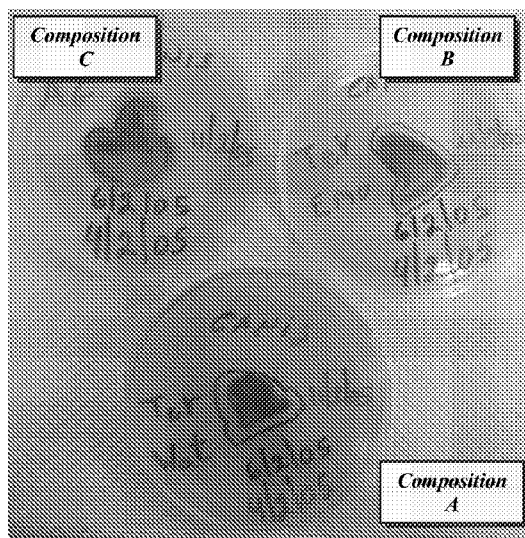


Fig. 1D

## FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 12/767,511, filed on Apr. 26, 2010, which is a continuation of and claims the benefit of priority under 35 U.S.C. §120 to U.S. patent application Ser. No. 11/430,599, filed on May 9, 2006, now U.S. Pat. No. 7,704,518, entitled "Foamable Vehicle and Pharmaceutical Compositions Thereof," which claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 60/679,020, filed on May 9, 2005, entitled "Hygroscopic Anti-Infective Compositions" and of U.S. Provisional Patent Application No. 60/784,793, filed on Mar. 21, 2006, entitled "Polyol Foamable Vehicle and Pharmaceutical Compositions Thereof," and which is a continuation-in-part application of U.S. patent application Ser. No. 10/835,505, filed on Apr. 28, 2004, now U.S. Pat. No. 7,820,145, which claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Patent Application Ser. No. 60/530,015, filed on Dec. 16, 2003, and U.S. Patent Application Ser. No. 60/492,385, filed on Aug. 4, 2003, all entitled "Oleaginous Pharmaceutical Foam" and all of which are hereby incorporated in their entirety by reference.

### BACKGROUND OF THE INVENTION

[0002] This invention relates to foamable pharmaceutical and cosmetic compositions.

[0003] External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, retinoid and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds.

[0004] Foams and, in particular, foams that are substantially based on non-aqueous solvents are complicated systems which do not form under all circumstances. US Pat. Appl. No. 20050031547 relates to stable oleaginous cosmetic or therapeutic foam compositions containing certain active agents, having unique therapeutic properties and methods of treatment using such compositions. The foamable carrier includes at least one solvent selected from a hydrophobic solvent, a silicone oil, an emollient, a co-solvent, and mixtures thereof, wherein the solvent is present at a concentration of about 70% to about 96.5% by weight of the total composition, at least a non-ionic surface-active agent at a concentration of about 0.1% to less than about 10% by weight of the total composition; at least one gelling agent at a concentration

of about 0.1% to about 5% by weight of the total composition; a therapeutically effective amount of at least one active agent; and at least one liquefied or compressed gas propellant, at a concentration of about 3% to about 25% by weight of the total composition.

[0005] WO 00/09082 teaches an anhydrous cleansing composition for topical application to human skin, comprising an ionic surfactant, glycerine, propylene glycol and water insoluble benefit agents. According to the examples of WO 00/09082, the concentration of the ionic surfactant is in the range of 18-22%.

[0006] U.S. Pat. No. 6,765,001 comprises a composition, method of enhancing potency and method of delivering corticosteroids in a vehicle comprising two or more penetration enhancers selected from the group consisting of diisopropyl adipate, dimethyl isosorbide, propylene glycol, 1,2,6-hexapetrol, and benzyl alcohol; and one or more of the group consisting of solvents and emulsifiers.

[0007] WO91/11991 teaches an essentially non-aqueous and non-oily foamable composition, that can be used for rectal administration of pharmaceuticals, comprising a liquid polar polyol or polyol mixture, a pharmaceutically active ingredient and at least one foam stabilizing and emulsifying surfactant. However, this foam composition is associated with disadvantages and the purposes of the present invention are not attained (see comparative example below).

[0008] There remains an unmet need for improved, easy to use, stable and non-irritating anti-infective foam formulations, intended for treatment of dermal and mucosal tissues. Particularly, there remains an unmet need for improved, easy to use, stable and non-irritating anti-infective foam formulations, with unique therapeutic properties.

### SUMMARY OF THE INVENTION

[0009] In one aspect, the invention provides a hygroscopic pharmaceutical composition including at least one hygroscopic substance at a sufficient concentration to provide an Aw value of the hygroscopic pharmaceutical composition of less than 0.9 and an anti-infective agent; or the Aw value is in the range of about 0.8 and about 0.9; (2) about 0.7 and about 0.8; and (3) less than about 0.7

[0010] In one or more embodiments, the hygroscopic pharmaceutical composition further includes at least one component, selected from the group consisting of about 0.01% to about 5% by weight of at least one polymeric agent selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and about 0.2% to about 5% by weight of a surface-active agent.

[0011] In one or more embodiments, the hygroscopic substance is selected from the group consisting of polyethylene glycols (PEGs), surfactants comprising PEG, polyols, monosaccharides, disaccharides, oligosaccharides and sugar alcohols in an amount to provide hygroscopic properties, and honey.

[0012] In another aspect, the invention provides a foamable pharmaceutical carrier including about 50% to about 98% of a polar solvent selected from the group consisting of (1) a polyol and (2) a polyethylene glycol (PEG); 0% to about 48% of a secondary polar solvent; about 0.2% to about 5% by weight of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent; and a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0013]** In one or more embodiments, the compositions further comprise up to 10% of water.

**[0014]** In one or more embodiments, the composition is substantially non-aqueous and/or substantially alcohol-free.

**[0015]** In one or more embodiments, the composition further comprises a therapeutically effective concentration of one or more active agents.

**[0016]** In one or more embodiments, the polyol is selected from the group consisting of a diol, a triol and a saccharide, and the triol may be selected from the group consisting of glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol, or the diol is selected from the group consisting of propylene glycol, butanediol, butenediol, butynediol, pentanediol, hexanediol, octanediol, neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

**[0017]** In one or more embodiments, the polyol consists of at least one diol and at least one triol, and wherein the ratio between the diol and triol is between 9:1 and 1:1.

**[0018]** In one or more embodiments, the composition includes a mixture of at least one polyol and at least one PEG, and the PEG may be selected from the group consisting of PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 4000, PEG 6000 and PEG 8000, or the composition contains one or more PEGs in a concentration to provide viscosity of less than 12,000 CPs.

**[0019]** In one or more embodiments, the composition includes a secondary polar solvent selected from the group consisting of dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol, ether, DMSO, a pyrrolidone, N-Methyl-2-pyrrolidone, 1-Methyl-2-pyrrolidinone, ethyl proxitol, dimethylacetamide, a PEG-type surfactant, an alpha hydroxy acid, lactic acid and glycolic acid, or the secondary polar solvent is dimethyl isosorbide.

**[0020]** In one or more embodiments, the composition includes (1) at least one polar solvent selected from a diol, a triol and PEG, and (2) at least one secondary polar solvent, and for example, the polar solvent comprises a mixture of at least one polyol and at least one PEG, and for example, the polyol comprises a mixture of at least two polyols.

**[0021]** In one or more embodiments, the ratio between the polyol and/or PEG and the secondary polar solvent is between 9:1 and 1:1.

**[0022]** In another aspect of the invention, a method of treating a disorder of mammalian subject includes administering a foamable therapeutic composition to a target area, the composition comprising a therapeutically effective concentration of an active agent, about 50% to about 98% of a polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol; 0% to about 48% of a secondary polar solvent; about 0.2% to about 5% by weight of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent; and a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0023]** In one or more embodiments, the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0024]** Various objects, features, and advantages of the present invention can be more fully appreciated with reference to the following detailed description of the invention

when considered in connection with the following drawings, in which like reference numerals identify like elements. The following drawings are for the purpose of illustration only and are not intended to be limiting of the invention, the scope of which is set forth in the claims that follow.

**[0025]** FIG. 1A-D illustrates the in vitro effect of effect of Composition A, consisting of 2% terbinafine, 95.3% gr. polyethylene glycol, 0.5% hydroxypropyl cellulose and 2.2% steareth-2, in comparison with Composition B (an oil in water emulsion containing 2% terbinafine) and Composition C a commercial 1% bifonazole cream, in the treatment of three fungal strains (*microsporium canis*, *trichophyton mentagrophytes* and *trichophyton rubrum*) and one yeast (*candida albicans*).

#### DETAILED DESCRIPTION OF THE INVENTION

**[0026]** The present invention relates to a composition for use as foamable vehicle composition.

**[0027]** According to one or more embodiments of the present invention, the foamable carrier, includes:

**[0028]** a. about 50% to about 98% of a polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

**[0029]** b. 0% to about 48% of a secondary polar solvent;

**[0030]** c. about 0.2% to about 5% by weight of a surface-active agent;

**[0031]** d. about 0.01% to about 5% by weight of at least one polymeric agent; and

**[0032]** e. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

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

**[0033]** Water, up to 25% of the composition, and more preferably up to 10%, and optional ingredients are added to complete the total mass to 100%. In certain cases, the composition contains two active agents that require different pH environments in order to remain stable. For example, corticosteroids are typically stable at acidic pH (they have a maximum stability at a pH of about 4-6) and vitamin D analogues are typically stable at basic pH (they have a maximum stability at pH values above about 8). In other cases, the active agent degrades in the presence of water, and therefore, in such cases the present of water in the composition is not desirable. Thus, in certain preferred embodiments, the composition is substantially non-aqueous. The term "substantially non-aqueous" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%.

**[0034]** Upon release from an aerosol container, the foamable carrier forms an expanded foam suitable for the treatment of an infected surface and for topical administration to the skin, a body surface, a body cavity or a mucosal surface.

**[0035]** The identification of a "polar 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 part in the foamable compositions described herein.

## Polyol

**[0036]** In an embodiment of the present invention, the polar solvent is a polyol. A polyol is an organic substance that contains at least two hydroxy groups in its molecular structure.

**[0037]** In one or more embodiments, the foamable carrier contains at least one diol (a compound that contains two hydroxy groups in its molecular structure). Examples of diols include propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butanediol (e.g., 1,2-butanediol, 1,3-butanediol, 2,3-butanediol and 1,4-butanediol), butanediol (e.g., 1,3-butanediol and 1,4-butanediol), butynediol, pentanediol (e.g., pentane-1,2-diol, pentane-1,3-diol, pentane-1,4-diol, pentane-1,5-diol, pentane-2,3-diol and pentane-2,4-diol), hexanediol (e.g., hexane-1,6-diol hexane-2,3-diol and hexane-2,5,6-diol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

**[0038]** In one or more embodiments, the foamable carrier contains at least one triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol.

**[0039]** In one or more embodiments, the polyol is a mixture of polyols. In one or more embodiments, the mixture of polyols contains at least one diol and at least one triol. According to certain embodiments the ratio between the diol and triol is between 9:1 and 1:1.

**[0040]** In one or more embodiments, part of mixture of polyols is a saccharide. Exemplary saccharides include, but are not limited to monosaccharide, disaccharides, oligosaccharides and sugar alcohols.

**[0041]** A monosaccharide is a simple sugar that cannot be hydrolysed to smaller units. Empirical formula is  $(CH_2O)_n$  and range in size from trioses ( $n=3$ ) to heptoses ( $n=7$ ). Exemplary monosaccharide compounds are ribose, glucose, fructose and galactose.

**[0042]** Disaccharides are made up of two monosaccharides joined together, such as sucrose, maltose and lactose.

**[0043]** A sugar alcohol (also known as a polyol, polyhydric alcohol, or polyalcohol) is a hydrogenated form of saccharide, whose carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group. They are commonly used for replacing sucrose in foodstuffs, often in combination with high intensity artificial sweeteners to counter the low sweetness. Some exemplary sugar alcohols, which are suitable for use according to the present invention are mannitol, sorbitol, xylitol, maltitol, lactitol. (Maltitol and lactitol are not completely hydrogenated compounds—they are a monosaccharide combined with a polyhydric alcohol). Mixtures of polyols, including (1) at least one polyol selected from a diol and a triol; and (2) a saccharide are contemplated within the scope of the present invention.

## Polyethylene Glycol

**[0044]** In an embodiment of the present invention, the polar solvent consists of a polymerized ethylene glycol, namely polyethylene glycol, which is also termed "PEG". Exemplary PEGs are provided in the following table.

Composition	Av. Molecular weight	Appearance	Melting point (° C.)
PEG 200	190~210	Oily liquid	
PEG 300	285~315	Oily liquid	
PEG 400	380~420	Oily liquid	
PEG 600	570~630	Oily liquid	17~22
PEG 1000	950~1050	Solid	35~40
PEG 4000	3800~4400	Solid	53~58
PEG 6000	5600~6400	Solid	55~60
PEG 8000	7500~8500	Solid	58~65

**[0045]** Thus, in an embodiment of the present invention, the PEG is selected from the group consisting of PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 4000, PEG 6000 and PEG 8000. The foamable carrier according to the present invention can contain a single PEG or a mixture of two or more PEGs. PEGs having molecular weight of more than that about 1000 possess gelling properties; i.e., they increase the viscosity of a composition. Therefore, by combining PEGs with different molecular weights/melting points, one can attain varying levels of flowability as desirable for the treatment of a given target site. The concentration of the PEG should be in a level that results in viscosity, prior to filling of the composition into aerosol canisters, of less than 12,000 CPs, and more preferably, less than 10,000 CPs.

## Secondary Polar Solvent

**[0046]** Optionally, a secondary polar solvent is added to the foamable composition of the present invention. The secondary polar solvent is selected from a variety of organic solvents that are typically miscible on both water and oil. Examples of polar solvent that can be contained in the foamable carrier of the present invention include dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol ether (glycofurol), DMSO, pyrrolidones, (such as N-Methyl-2-pyrrolidone and 1-Methyl-2-pyrrolidinone), ethyl proxitol, dimethylacetamide (DMAc), PEG-type surfactants and alpha hydroxy acids, such as lactic acid and glycolic acid.

Solubilization and Penetration Enhancement In many cases, polyols, PEGs and polar solvents possess a high solubilizing power and thus, they can enable increased concentrations of a pharmaceutical active agent. Polyols, PEGs and polar solvents are also known for their skin penetration enhancement properties. These properties enable high drug bioavailability in the target area of treatment, resulting in an enhanced therapeutic effect. Occasionally, combinations of a polyol, PEGs and a secondary polar solvent, exhibit an increased permeability across the skin, as suggested, for example, in Eur J Pharm Biopharm. 1998 November; 46(3):265-71.

**[0047]** Thus, in one or more embodiments, the foamable carrier contains (1) at least one polar solvent, selected from a polyol (selected from a diol and a triol) and PEG; and (2) at least one secondary polar solvent.

**[0048]** In one or more embodiments, the foamable carrier contains (1) a mixture of at least two polyols; and (2) at least one secondary polar solvent. In additional embodiments, the foamable carrier contains a mixture of at least one polyol and at least one PEG; yet in other embodiments the foamable carrier contains (1) a mixture of at least one polyol and at least one PEG and (2) at least one secondary polar solvent.

**[0049]** According to certain embodiments the ratio between the polyol and/or PEG and the secondary polar solvent is between 9:1 and 1:1.

**[0050]** In certain embodiments, the polyol is selected from the group consisting of propylene glycol, hexylene glycol and glycerin (and mixtures thereof); and the secondary polar solvent is selected from the group consisting of dimethyl isosorbide, diethylene glycol monoethyl ether, a liquid polyethylene glycol and glycofurol.

**[0051]** In certain embodiments, the foamable carrier contains (1) at least one polyol; and (2) dimethyl isosorbide.

**[0052]** Short chain alcohols, such as ethanol and propanol are known as polar solvents, however, according to one or more embodiments, the composition of the present invention 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 polar solvents due to their skin-irritating effect.

**[0053]** Thus, in certain 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%. However, in other embodiments, a short chain alcohol can be included in the composition, as long as the ratio between the short chain alcohol and the polyol is less than 1:4 by weight.

#### Polymeric Agent

**[0054]** The composition of the present invention contains a polymeric agent. It has been documented that the presence of a polymeric agent is necessary for the creation of foam, having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ. Preferably, the polymeric agent is soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent.

**[0055]** Non-limiting examples of polymeric agents that are soluble or readily dispersible in propylene glycol are Hydroxypropylcellulose and carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981.

**[0056]** Other polymeric agents are suitable for use according to the present invention provided that they are soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent, on a case by case basis.

**[0057]** Exemplary polymeric agents include, in a non-limiting manner, 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, cationic guar, hydroxypropyl guar gum, starch, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

**[0058]** Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, methylhydroxyethylcellulose, meth-

ylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, and cationic celluloses. Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar solvents", as detailed herein, they are also considered polymeric agents.

**[0059]** Mixtures of the above polymeric agents are contemplated.

**[0060]** The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

#### Surface-Active Agent

**[0061]** The composition of the present invention 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).

**[0062]** According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 12, or more than one surface active agent and the weighted average of their HLB values is between about 7 and about 12.

**[0063]** Preferably, the composition of the present invention contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include polysorbates, such as polyoxyethylene (20) sorbitan monostearate (Tween 60) and poly(oxyethylene) (20) sorbitan monooleate (Tween 80); poly(oxyethylene) (POE) fatty acid esters, such as Myrj 45, Myrj 49, Myrj 52 and Myrj 59; poly(oxyethylene)alkyl ether, such as poly(oxyethylene)cetyl ether, poly(oxyethylene)palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1; sucrose esters, partial esters of sorbitol and its anhydrides, such as sorbitan monolaurate and sorbitan monolaurate; mono or diglycerides, isoceteth-20, and mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters).

**[0064]** Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include PEG 100 stearate (HLB=11), Laureth 4 (HLB=9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

**[0065]** Yet, in additional embodiments, the composition contains a single surface active agent or a combination of surface active agents having an HLB values between about 9 and about 14; and in other embodiments, the composition contains one or more surface active agents, having an HLB value between about 2 and about 9.

**[0066]** 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.

**[0067]** In one or more embodiments of the present invention, 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. We have surprisingly found that non-ionic surfactants alone provide foams of excellent quality, i.e. a score of "E" according to the grading scale discussed herein below.

**[0068]** Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant, or 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 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. The concentration of the surface active agent is between about 0.1% and about 5%.

#### Hydrophobic Solvent

**[0069]** Optionally, the foamable carrier further contains at least one hydrophobic solvent. The identification of a "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 part in the foamable compositions described herein.

**[0070]** A "hydrophobic solvent" 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 preferably less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL.

**[0071]** In one or more embodiments, the hydrophobic organic carrier is an oil, such as mineral oil, 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, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzgium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxanes, polyaryl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers, polydimethylsiloxanes (dimethicones) and poly(dimethylsiloxane)-(diphenyl-siloxane) copolymers.

#### Foam Adjuvant

**[0072]** Optionally, a foam adjuvant is included in the foamable carriers of the present invention to increase the foaming

capacity of surfactants and/or to stabilize the foam. In one or more embodiments of the present invention, 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.

**[0073]** In one or more embodiments of the present invention, 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.

**[0074]** 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.

#### Additional Components

**[0075]** In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

**[0076]** In an embodiment of the present invention, the additional component is a pH adjusting agent or a buffering agent. Suitable buffering agents include but are not limited to acetic acid, adipic acid, calcium hydroxide, citric acid, glycine, hydrochloric acid, lactic acid, magnesium aluminummetasilicates, phosphoric acid, sodium carbonate, sodium citrate, sodium hydroxide, sorbic acid, succinic acid, tartaric acid, and derivatives, salts and mixtures thereof.

**[0077]** In an embodiment of the present invention, the additional component is an emollient. Suitable emollients include but are not limited to mineral oil, lanolin oil, coconut oil, cocoa butter, olive oil, aloe vera extract, jojoba oil, castor oil, fatty acids, fatty alcohols, diisopropyl adipate, hydroxybenzoate esters, benzoic acid esters of C9 to C15 alcohols, isononyl iso-nonanoate, silicone oils, polyethers, C12 to C15 alkyl benzoates, oleic acid, stearic fatty acid, cetyl alcohols, hexadecyl alcohol, dimethyl polysiloxane, polyoxypropylene

cetyl ether, polyoxypropylene butyl ether, and derivatives, esters, salts and mixtures thereof.

**[0078]** In an embodiment of the present invention, the additional component is a humectant. Suitable humectants include but are not limited to guanidine, urea, glycolic acid, glycolate salts, ammonium glycolate, quaternary alkyl ammonium glycolate, lactic acid, lactate salts, ammonium lactate, quaternary alkyl ammonium lactate, aloe vera, aloe vera gel, allantoin, urazole, alkoxylated glucose, hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine and derivatives, esters, salts and mixtures thereof.

**[0079]** In an embodiment of the present invention, the additional component is a preservative. Suitable preservatives include but are not limited to C12 to C15 alkyl benzoates, alkyl p-hydroxybenzoates, aloe vera extract, ascorbic acid, benzalkonium chloride, benzoic acid, benzoic acid esters of C9 to C15 alcohols, butylated hydroxytoluene, castor oil, cetyl alcohols, chlorocresol, citric acid, cocoa butter, coconut oil, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, DMDM hydantoin, ethanol, fatty acids, fatty alcohols, hexadecyl alcohol, hydroxybenzoate esters, iodopropynyl butylcarbamate, isononyl iso-nonanoate, jojoba oil, lanolin oil, methylparaben, mineral oil, oleic acid, olive oil, polyethers, polyoxypropylene butyl ether, polyoxypropylene cetyl ether, potassium sorbate, silicone oils, sodium propionate, sodium benzoate, sodium bisulfite, sorbic acid, stearic fatty acid, vitamin E, vitamin E acetate and derivatives, esters, salts and mixtures thereof.

**[0080]** In an embodiment of the present invention, the additional component is a skin penetration enhancer. Suitable skin penetration enhancers include but are not limited to acetone, acyl lactylates, acyl peptides, acylsarcosinates, alkanolamine salts of fatty acids, alkyl benzene sulphonates, alkyl ether sulphonates, alkyl sulphates, anionic surface-active agents, benzyl benzoate, benzyl salicylate, butan-1,4-diol, butyl benzoate, butyl laurate, butyl myristate, butyl stearate, cationic surface-active agents, citric acid, cocoamidopropylbetaine, decyl methyl sulfoxide, decyl oleate, dibutyl azelate, dibutyl phthalate, dibenzyl sebacate, dibutyl sebacate, dibutyl suberate, dibutyl succinate, dicapryl adipate, didecyl phthalate, diethylene glycol, diethyl sebacate, diethyl-m-toluamide, di(2-hydroxypropyl)ether, diisopropyl adipate, diisopropyl sebacate, N,N-dimethyl acetamide, dimethyl azelate, N,N-dimethyl formamide, 1,5-dimethyl-2-pyrrolidone, dimethyl sebacate, dimethyl sulphoxide, dioctyl adipate, dioctyl azelate, dioctyl sebacate, 1,4 dioxane, 1-dodecylazacycloheptan-2-one, dodecyl dimethyl amine oxides, ethyl caprate, ethyl caproate, ethyl caprylate, 2-ethyl-hexyl pelargonate, ethyl-2-hydroxypropanoate, ethyl laurate, ethyl myristate, 1-ethyl-2-pyrrolidone, ethyl salicylate, hexyl laurate, 2-hydroxyoctanoic acid, 2-hydroxypropanoic acid, 2-hydroxypropionic acid, isethionates, isopropyl isostearate, isopropyl palmitate, guar hydroxypropyltrimonium chloride, hexan-2,5-diol, khellin, lamepons, lauryl alcohol, maypons, metal salts of fatty acids, methyl nicotinate, 2-methyl propan-2-ol, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, methyl taurides, miranol, nonionic surface-active agents, octyl alcohol, octylphenoxy polyethoxyethanol, oleic ethanolamide, pleyl alcohol, pentan-2,4-diol, phenoxyethanol, phosphatidyl choline, phosphine oxides, polyalkoxylated ether glycolates, poly(diallylpiperidinium chloride), poly(dipropyldiallylammonium chloride), polyglycerol esters, polyoxyethylene lauryl ether, polyoxy:polyoxyethylene stearate, polyoxypropylene 15 stearyl ether, poly(vinyl pyridinium chloride),

propan-1-ol, propan-2-ol, propylene glycol dipelargonate, pyroglutamic acids, 2-pyrrolidone, pyruvic acids, Quaternium 5, Quaternium 18, Quaternium 19, Quaternium 23, Quaternium 31, Quaternium 40, Quaternium 57, quaternary amine salts, quaternised poly (dimethylaminoethylmethacrylate), quaternised poly (vinyl alcohol), sapamin hydrochloride, sodium cocaminopropionate, sodium dioctyl sulphosuccinate, sodium laurate, sodium lauryl ether sulphate, sodium lauryl sulphate, sugar esters, sulphosuccinate, tetrahydrofuran, tetrahydrofurfural alcohol, transcitol, triethanolamine dodecyl benzene sulphonate, triethanolamine oleate, urea, water and derivatives, esters, salts and mixtures thereof.

#### Propellants

**[0081]** Examples of suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

**[0082]** In certain embodiments, 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.

**[0083]** Such propellants include, but are not limited to hydrofluorocarbon (HFC) propellants, that contain no chlorine atoms, and as such, falls completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluoroethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227), 1,1, difluoro ethane (Dymel 152) and 1,1,1,3,3,3 hexafluoropropane. HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

**[0084]** The propellant makes up about 5-25 wt % of the foamable composition. Aerosol propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

#### Hygroscopic Property of the Composition

**[0085]** A hygroscopic substance is a substance that absorbs water readily from its surroundings. Microorganisms require water to grow and reproduce, and such water requirements are best defined in terms of water activity of the substrate. The water activity of a solution is expressed as  $A_w = P/P_o$ , where P is the water vapor pressure of the solution and  $P_o$  is the vapor pressure of pure water at the same temperature. Addition of a hygroscopic substance to an aqueous solution in which a microorganism is growing will have the effect of lowering the  $A_w$ , with a consequent effect upon cell growth. Every microorganism has a limiting  $A_w$ , below which it will not grow, e.g., for streptococci, *klebsiella* spp., *escherichia coli*, *clostridium perfringens*, and *pseudomonas* spp. the  $A_w$  value is 0.95. *Staphylococcus aureus* is most resistant and can proliferate with an  $A_w$  as low as 0.86.

**[0086]** The water activity of a product can be determined from the relative humidity of the air surrounding the sample when the air and the sample are at equilibrium. Measurement is performed by placing a sample in an enclosed space where this equilibrium can take place. Once this occurs, the water



activity of the sample and the relative humidity of the air are equal. The measurement taken at equilibrium is called an equilibrium relative humidity or ERH. The relationship between the water activity and ERH is in accordance with the following formula:

$$A_w = ERH/100$$

**[0087]** Various types of water activity instruments are commercially available. One exemplary instrument uses chilled-mirror dewpoint technology while other instruments measure relative humidity with sensors that change electrical resistance or capacitance.

**[0088]** Polyols, PEGs and other polar solvents have a great affinity for water, and as such, they exhibit hygroscopic properties. The concentration of the polyol, the PEG and/or other polar solvents determines the  $A_w$  of the carrier. In one or more embodiments, the polyols, the PEG and/or the secondary polar solvent is contained in the composition of the present invention at a sufficient concentration to provide an  $A_w$  value of the hygroscopic carrier of less than 0.9. In other embodiments, the concentration of the polyol, the PEG and/or secondary polar solvent in the composition is selected to provide a  $A_w$  value selected from the ranges of (1) about 0.8 and about 0.9; (2) about 0.7 and about 0.8; and (3) less than about 0.7.

**[0089]** As such, a composition containing a polyol, a PEG with or without a secondary polar solvent can be used as topical treatment of superficial infectious conditions.

**[0090]** The advantage of providing a hygroscopic composition in a pressurized packaging presentation is readily perceived. The usage of all other presentations, such as solutions, creams, lotions, ointments and the like involves repeated opening of the package closure, resulting in absorption of water from the surrounding environment and a subsequent elevation of the  $A_w$  (thus lowering the hygroscopicity of the product, and therefore decreasing its anti-infective potential. By contrast, a pressurized packaging does not allow for any humidity to be absorbed by the preparation, and therefore, the hygroscopic character of the composition cannot be damaged.

**[0091]** In one or more embodiments, the hygroscopic composition of the present invention further contains an anti-infective agent, selected from the group of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent. Combining the anti-infective effect of a hygroscopic composition, which acts through a dehydration mechanism, with an additional anti-infective agent that acts through alternate mechanisms results in a synergistic effect and consequently higher success rate of the treatment.

#### Composition and Foam Physical Characteristics and Advantages

**[0092]** A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention 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.

**[0093]** The foamable composition of the present invention is stable, having an acceptable shelf-life of at least one year, or preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. Organic carriers and

propellants tend to impair the stability of emulsions and to interfere with the formation of stable foam upon release from a pressurized container. It has been observed, however, that the foamable 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.

**[0094]** 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.

**[0095]** Foam quality can be graded as follows:

**[0096]** 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.

**[0097]** 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.

**[0098]** 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.

**[0099]** 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.

**[0100]** Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

**[0101]** Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

**[0102]** Typically administrable 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.

**[0103]** As further aspect of the foam is breakability. The breakable foam is thermally stable, yet breaks 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, therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

**[0104]** The foam of the present invention has several advantages, when compared with hydroalcoholic foam compositions, such as described in WO 2004/071479:

**[0105]** (1) Breakability. The foam of the present invention is thermally stable. Unlike hydroalcoholic foam compositions of the prior art, the foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, since it allows comfortable application and well directed administration to the target area.

**[0106]** (2) Skin drying and skin barrier function. Short chain alcohols are known to dry the skin and impair the integrity of the skin barrier. By contrast, including a film forming agent in the composition of the present invention does not cause unwanted skin barrier damage.

[0107] (3) Irritability. Due to the lack of alcohol and improvement in skin barrier function, skin irritability is eliminated.

[0108] Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

#### Pharmaceutical Composition

[0109] The foamable composition of the present invention is an ideal vehicle for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents". A foamable composition, comprising an active agent has the following advantages:

- [0110] 1. The foamable composition provides a preferred solvent for active agents, particularly water-insoluble agents.
- [0111] 2. The inclusion of a polyol and/or a PEG and a secondary polar solvent in the foamable composition facilitates a co-solvent effect, resulting increased concentrations of soluble active agent in the dosage form, thus facilitating enhanced skin penetration of the active agent. In many cases, increased penetration is positively correlated with improved clinical outcome. In certain case, attaining an increased drug penetration into the target site of action enables a decrease of treatment frequency, for example, from twice or three times daily to once daily.
- [0112] 3. Polyols and PEGs; and combinations of a polyol and/or PEG with a secondary polar solvent are known as skin penetration enhancers, thus, increasing drug residence in the target area and increasing clinical efficacy, as detailed above.
- [0113] 4. The fact that the composition contains no water, or up to 25% and more preferably up to 10% water minimizes the probability of degradation of water-sensitive active agents. Furthermore, as exemplified herein, a foam containing a polyol and/or PEG with no water at all can be formed in accordance with the composition and process of the present invention. Such compositions ensure high stability of water sensitive active agents.
- [0114] 5. Combining the anti-infective effect of a hygroscopic composition, which acts through a dehydration mechanism, with an additional anti-infective agent, selected from the group of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent, that acts through alternate mechanisms results in a synergistic effect and consequently higher success rate of the treatment.
- [0115] 6. The foamable polyol composition in contained in an impermeable pressurized packaging presentation is impermeable and thus, the active agent is not exposed to environmental degradation factors, such as light and oxidating agent during storage.
- [0116] Thus, in a preferred embodiment of the present invention, the composition includes at least one active agent.
- [0117] a. a therapeutically effective concentration of an active agent; and

[0118] b. about 50% to about 98% of a polar solvent, selected from the group consisting of a polyol and a polyethylene glycol;

[0119] c. 0% to about 48% of a secondary polar solvent;

[0120] d. about 0.2% to about 5% by weight of a surface-active agent;

[0121] e. about 0.01% to about 5% by weight of at least one polymeric agent; and

[0122] f. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

[0123] In the context of combining a hygroscopic carrier according to the present invention and an anti-infective active agent, a pharmaceutical composition is provided, including:

[0124] a. a hygroscopic substance at a sufficient concentration to provide an  $A_w$  value of the hygroscopic carrier of less than 0.9. The concentration of the hygroscopic substance in the composition can be designed to provide a  $A_w$  value selected from the ranges of (1) about 0.8 and about 0.9; (2) about 0.7 and about 0.8; and (3) less than about 0.7.;

[0125] b. about 0.2% to about 5% by weight of a surface-active agent;

[0126] c. about 0.01% to about 5% by weight of at least one polymeric agent selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

[0127] d. a therapeutically effective concentration of an anti-infective agent; and

[0128] e. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

[0129] An exemplary case for the inclusion of an anti-infective agent in a hygroscopic composition is provided herewith. It has been surprisingly discovered that combining an antifungal agent in a hygroscopic composition results in an anti-infective effect on strains that are not supposed to be affected by the said antifungal agent. For example, terbinafine is known to be highly effective against dermatophyte pathogens, but not against candida. In-vitro studies have revealed, however that terbinafine, dissolved in a hygroscopic carrier, effectively inhibited the spreading of *candida albicans*, while a control preparation, comprising the same concentration of terbinafine in an emulsion base was not effective. Thus, combining an antifungal agent in a hygroscopic composition results in an expansion of the spectrum of infective strains that can benefit from the therapy, and furthermore, in can render an improved effect of such a composition on mixed infections or in infections that are not accurately diagnosed.

[0130] Consequently, in another aspect of the present invention, a pharmaceutical composition, which possesses an improved antifungal activity or that possesses an antifungal activity on an expanded spectrum of pathogens, is provided, including:

[0131] a. a hygroscopic composition, comprising a hygroscopic substance at a sufficient concentration to provide an  $A_w$  value of the hygroscopic carrier of less than 0.9. The concentration of the hygroscopic substance in the composition can be designed to provide a  $A_w$  value selected from the ranges of (1) about 0.8 and about 0.9; (2) about 0.7 and about 0.8; and (3) less than about 0.7;

[0132] b. an anti-infective agent, selected from the group of an antibiotic agent, an antibacterial agent, an antifun-

gal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent. Preferably, the anti-infective agent is an antifungal agent, and more preferably the anti-infective agent is terbinafine.

#### Active Agents

**[0133]** Suitable active agents include but are not limited to active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, anti-acne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidan-druff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilepemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, anti-swelling agents, antiviral agents, antiyeast agents, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

**[0134]** In an embodiment of the present invention, the active agent is an active herbal extract. Suitable active herbal extracts include but are not limited to angelica, anise oil, astragali radix, azalea, benzyl acetate, birch tar oil, bornyl acetate, cacumen biotae, camphor, cantharidin, *capsicum*, cineole, cinnamon bark, cinnamon leaf, citronella, citronellol, citronellyl acetate, citronellyl formate, eucalyptus, eugenyl acetate, flos carthami, fructus mori, garlic, geraniol, geranium, geranyl acetate, habanera, isobutyl angelicate, lavender, ledum latifolium, ledum palustre, lemongrass, limonene, linalool, linalyl acetate, methyl anthranilate, methyl cinnamate, mezereum, neem, nerol, nerol acetate, nettle root extract, oleum ricini, oregano, pinenes, .alpha.-pinene, .beta.-pinene, radix angelicae sinensis, radix paenoniae rubra, radix polygoni multiflori, radix rehmanniae, rhizoma pinelliae, rhizoma zingiberis recens, sabadilla, sage, sandalwood oil, saw palmetto extract, semen sesami nigrum, stapysagria, tea tree oil, terpene alcohols, terpene hydrocarbons, terpene esters, terpinene, terpineol, terpinyl acetate and derivatives, esters, salts and mixtures thereof. In an embodiment of the present invention, the active agent is an acaricide. Suitable acaricides include but are not limited to amitraz, flumethrin, fluralinate and derivatives, esters, salts and mixtures thereof.

**[0135]** In an embodiment of the present invention, the active agent is an age spot and keratoses removing agent. Suitable age spot and keratoses removing agent include but are not limited to hydroxy acids, azelaic acid and other related dicarboxylic acids, retinoids, kojic acid, arbutin, nicotinic, ascorbic acid, hydroquinone and derivatives, esters, salts and mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as diclofenac are also useful for the treatment of keratoses.

**[0136]** In an embodiment of the present invention, the active agent is an analgesic. Suitable analgesics include but are not limited to benzocaine, butamben picrate, dibucaine, dimethisoquin, dyclonine, lidocaine, pramoxine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

**[0137]** In an embodiment of the present invention, the active agent is a local anesthetic. Suitable local anesthetics include but are not limited to benzocaine, benzyl alcohol, bupivacaine, butamben picrate, chlorprocaine, cocaine, dibucaine, dimethisoquin, dyclonine, etidocaine, hexylcaine, ketamine, lidocaine, mepivacaine, phenol, pramoxine, procaine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

**[0138]** In an embodiment of the present invention, the active agent is an antiacne agent. Suitable antiacne agents include but are not limited to N-acetylcysteine, adapalene, azelaic acid, benzoyl peroxide, cholate, clindamycin, deoxycholate, erythromycin, flavinoids, glycolic acid, meclocycline, metronidazol, mupirocin, octopirox, phenoxy ethanol, phenoxy propanol, pyruvic acid, resorcinol, retinoic acid, salicylic acid, scymmol sulfate, sulfacetamide-sulfur, sulfur, tazarotene, tetracycline, tretinoin triclosan and derivatives, esters, salts and mixtures thereof.

**[0139]** In an embodiment of the present invention, the active agent is an antiaging agent. Suitable antiaging agents include but are not limited to sulfur-containing D and L amino acids, alpha-hydroxy acids, beta-hydroxy acids (e.g. salicylic acid), urea, hyaluronic acid, phytic acid, lipoic acid; lysophosphatidic acid, skin peel agents (e.g., phenol, resorcinol and the like), vitamin B3 compounds (e.g., niacinamide, nicotinic acid and nicotinic acid salts and esters, including non-vasodilating esters of nicotinic acid (such as tocopheryl nicotinate), nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide), vitamin B5 and retinoids (e.g., retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, retinyl ascorbate) skin barrier forming agents, melatonin and derivatives, esters, salts and mixtures thereof.

**[0140]** In an embodiment of the present invention, the active agent is an antibiotic. The terms "antibiotic" as used herein shall include, but is not limited to, any substance being destructive to or inhibiting the growth of bacteria or any substance having the capacity to inhibit the growth of or to destroy bacteria. In one or more embodiments, the antibiotic agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, an antibiotic glycopeptide, a macrolide, an antibiotic nucleoside, an antibiotic peptide, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, a sulfonamide, an antibiotic metal, an oxidizing agent, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, a triguanide, a bisbiguanide, a polymeric biguanide, and analogs, derivatives, salts, ions and complexes thereof.

**[0141]** Suitable antibiotics include but are not limited to amfanfadin hydrochloride, amfanfadin sulfate, amikacin, amikacin sulfate, aminoglycosides, amoxicillin, ampicillin, ansamycins, bacitracin, beta-lactams, candicidin, capreomycin, carbenicillin, cephalixin, cephaloridine, cephalothin, cefazolin, cephapirin, cephradine, cephaloglycin, chloramphenicols, chlorhexidine, chlorhexidine gluconate, chlorhexidine hydrochloride, chloroxine, chlorquinaldol, chlo-

tetracycline, chlortetracycline hydrochloride, ciprofloxacin, circurin, clindamycin, clindamycin hydrochloride, clotrimazole, cloxacillin, demeclocycline, diclosxacillin, diiodohydroxyquin, doxycycline, ethambutol, ethambutol hydrochloride, erythromycin, erythromycin estolate, erythromycin stearate, farnesol, floxacillin, gentamicin, gentamicin sulfate, gramicidin, griseofulvin, haloprogin, haloquinol, hexachlorophene, iminocyclidine, iodate, iodine, iodochlorhydroxyquin, kanamycin, kanamycin sulfate, lincomycin, lineomycin, lineomycin hydrochloride, macrolides, meclocyline, methacycline, methacycline hydrochloride, methenamine, methenamine hippurate, methenamine mandelate, methicillin, metronidazole, miconazole, miconazole hydrochloride, microcrystalline and nanocrystalline particles of silver, copper, zinc, mercury, tin, lead, bismuth, cadmium and chromium, minocycline, minocycline hydrochloride, mupirocin, nafcillin, neomycin, neomycin sulfate, netilmicin, netilmicin sulfate, nitrofurazone, norfloxacin, nystatin, octopirox, oleandomycin, orcephalosporins, oxacillin, oxytetracycline, oxytetracycline hydrochloride, parachlorometa xyleneol, paromomycin, paromomycin sulfate, penicillins, penicillin G, penicillin V, pentamidine, pentamidine hydrochloride, phenethicillin, polymyxins, quinolones, streptomycin sulfate, tetracycline, tobramycin, tolnaftate, triclosan, trifampin, rifamycin, rolitetracycline, spectinomycin, spiramycin, streptomycin, sulfonamide, tetracyclines, tetracycline, tobramycin, tobramycin sulfate, triclocarbon, triclosan, trimethoprim-sulfamethoxazole, tylosin, vancomycin, yrothricin and derivatives, esters, salts and mixtures thereof.

**[0142]** In an embodiment of the present invention, the active agent is an antidandruff agent. Suitable antidandruff agents include but are not limited to aminexil, benzalkonium chloride, benzethonium chloride, 3-bromo-1-chloro-5,5-dimethyl-hydantoin, chloramine B, chloramine T, chlorhexidine, N-chlorosuccinimide, climbazole-, 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dichloro-5,5-dimethyl-hydantoin, betulonic acid, betulonic acid, celastrol, crataegolic acid, cromakalin, cyproterone acetate, dutasteride, finasteride, ibuprofen, ketoconazole, oleanolic acid, phenyloin, picrotone olamine, salicylic acid, selenium sulphides, triclosan, triiodothyronine, ursolic acid, zinc gluconate, zinc omadine, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

**[0143]** In an embodiment of the present invention, the active agent is an antihistamine. Suitable antihistamines include but are not limited to chlorcyclizine, diphenhydramine, mepyramine, methapyrilene, tripeleminamine and derivatives, esters, salts and mixtures thereof.

**[0144]** In an embodiment of the present invention, the active agent is an antimycotic. Also termed antifungal agent. The terms "antimycotic" and "antifungal" as used herein include, but is not limited to, any substance being destructive to or inhibiting the growth of fungi and yeast or any substance having the capacity to inhibit the growth of or to destroy fungi and/or yeast.

**[0145]** In one or more embodiments, the antifungal agent is an agent that is useful in the treatment of a superficial fungal infection of the skin, dermatophytosis, *microsporum*, *trichophyton* and *epidermophyton* infections, candidiasis, oral candidiasis (thrush), candidiasis of the skin and genital mucous membrane, *candida* paronychia, which inflicts the nail and nail bed and genital and vaginal *candida*, which inflict genitalia and the vagina.

**[0146]** Suitable antimycotics include but are not limited to allylamines, amorolfine, amphotericin B, azole compounds, bifonazole, butoconazole, chloroxine, clotrimazole, ciclopirox olamine, clotrimazole, econazole, elubiol, fenticonazole, fluconazole, flucytosine (5FC), griseofulvin, itraconazole, ketoconazole, mafenide acetate, miconazole, naftifine, natamycin, tolnaftate, nystatin, polyenes, oxiconazole, sulbentine, sulconazole, terbinafine, terconazole, tioconazole, undecylenic acid and derivatives, esters, salts and mixtures thereof.

**[0147]** In an embodiment of the present invention, the active agent is an antipruritic. Suitable antipruritics include but are not limited to menthol, methdilazine, trimeprazine, urea and derivatives, esters, salts and mixtures thereof.

**[0148]** In an embodiment of the present invention, the active agent is an additional antipsoriatic agent. Suitable additional antipsoriatic agents include but are not limited to 6-aminonicotinamide, 6-aminonicotinic acid, 2-aminopyrazinamide, anthralin, 6-carbamoylnicotinamide, 6-chloronicotinamide, 2-carbamoylpyrazinamide, corticosteroids, 6-dimethylaminonicotinamide, dithranol, 6-formylaminonicotinamide, 6-hydroxy nicotinic acid, 6-substituted nicotinamides, 6-substituted nicotinic acid, 2-substituted pyrazinamide, tazarotene, thionicotinamide, trichothecene mycotoxins and derivatives, esters, salts and mixtures thereof.

**[0149]** In an embodiment of the present invention, the active agent is an antirosacea agent. Suitable antirosacea agents include but are not limited to azelaic acid, metronidazole, sulfacetamide and derivatives, esters, salts and mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as salicylic acid, salicylates, piroxicam and diclofenac are also useful for the treatment of Rosacea.

**[0150]** In an embodiment of the present invention, the active agent is an antiseborrheic agent. Suitable antiseborrheic agents include but are not limited to glycolic acid, salicylic acid, selenium sulfide, zinc pyrithione, a dicarboxylic acid, such as azelaic acid and derivatives, esters, salts and mixtures thereof.

**[0151]** In an embodiment of the present invention, the active agent is an antiviral agent. Suitable antiviral agents include but are not limited to acyclovir, gancyclovir, ribavirin, amantadine, rimantadine nucleoside-analog reverse transcriptase inhibitors, such as zidovudine, didanosine, zalcitabine, tavudine, lamivudine and vidarabine, non-nucleoside reverse transcriptase inhibitors, such as nevirapine and delavirdine, protease inhibitors, such as saquinavir, ritonavir, indinavir and nelfinavir, and interferons and derivatives, esters, salts and mixtures thereof.

**[0152]** In an embodiment of the present invention, the active agent is a chemotherapeutic agent. Suitable chemotherapeutic agents include but are not limited to daunorubicin, doxorubicin, idarubicin, amrubicin, pirarubicin, epirubicin, mitoxantrone, etoposide, teniposide, vinblastine, vincristine, mitomycin C, 5-FU, paclitaxel, docetaxel, actinomycin D, colchicine, topotecan, irinotecan, gemcitabine cyclosporin, verapamil, valsopodol, probenecid, MK571, GF120918, LY335979, biricodar, terfenadine, quinidine, pervilleine A, XR9576 and derivatives, esters, salts and mixtures thereof.

**[0153]** In an embodiment of the present invention, the active agent is a corticosteroid. Suitable corticosteroids include but are not limited to alclometasone dipropionate, amcinafel, amcinafide, amcinonide, beclomethasone,

beclo-methasone dipropionate, betamethasone, betamethasone benzoate, betamethasone dexamethasone-phosphate, dipropionate, betamethasone valerate, budesonide, chlorprednisone, chlorprednisone acetate, clescinolone, clobetasol, clobetasol propionate, clobetasol valerate, clobetasone, clobetasone butyrate, clocortelone, cortisone, cortodoxone, crapsone butyrate, desonide, desoxymethasone, dexamethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, difluorosone diacetate, diffluprednate, fluadrenolone, flucetonide, flucloronide, fluclorolone acetonide, flucortine butylesters, fludroxycortide, fludrocortisone, flumethasone, flumethasone pivalate, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluosinolone acetonide, fluperolone, fluprednidene acetate, fluprednisolone hydrocortamate, fluradrenolone, fluradrenolone acetonide, flurandrenolone, fluticasone, halcinonide, halobetasol, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cyclopentylpropionate, hydrocortisone valerate, hydroxyltri-aminolone, medrysone, meprednisone, .alpha.-methyl dexamethasone, methylprednisolone, methylprednisolone acetate, mometasone furoate, paramethasone, prednisolone, prednisone, pregnenolone, progesterone, spironolactone, triamcinolone, triamcinolone acetonide and derivatives, esters, salts and mixtures thereof.

**[0154]** In an embodiment of the present invention, the active agent is a hair growth regulator. Suitable hair growth regulators include but are not limited to N-acetylgalactosamine, N-acetylglucosamine, N-acetylmannosamine, acitretin, aminexil, ascomycin, asiatic acid, azelaic acid, benzalkonium chloride, benzethonium chloride, benzydamine, benzyl nicotinate, benzoyl peroxide, benzyl peroxide, betulinic acid, betulonic acid, calcium pantothenate, celastrol, cepharanthine, chlorpheniramine maleate, clinacynin hydrochloride, crataegolic acid, cromakalin, cyproterone acetate, diazoxide, diphenhydramine hydrochloride, dutasteride, estradiol, ethyl-2-hydroxypropanoate, finasteride, D-fucono-1,5-lactone, furoate, L-galactono-1,4-lactone, D-galactosamine, D-glucaro-1,4-lactone, D-glucosamine-3-sulphate, hinokitiol, hydrocortisone, 2-hydroxypropionic acid, isotretinoin, itraconazole, ketoconazole, latanoprost, 2-methyl propan-2-ol, minocyclin, minoxidil, mipirocin, mometasone, oleanolic acid, panthenol, 1,10-phenanthroline, phenyloloin, prednisolone, progesterone, propan-2-ol, pseudoterins, resorcinol, selenium sulfide, tazarotene, triclocarbon, triclosan, triiodothyronine, ursolic acid, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

**[0155]** In an embodiment of the present invention, the active agent is a hormone. Suitable hormones include but are not limited to methyltestosterone, androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androsteronediol, androsteronediol-3-acetate, androsteronediol-17-acetate, androsteronediol 3-17-diacetate, androsteronediol-17-benzoate, androsteronedione, androstenedione, androstenediol, dehydroepiandrosterone, sodium dehydroepiandrosterone sulfate, dromostanolone, dromostanolone propionate, ethylestrenol, fluoxymesterone, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexane-propionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, androsteronediol-3-acetate-1-7-benzoate, oxandrolone, oxymetholone, stanozolol, testosterone, testosterone decanoate, 4-dihydrotestosterone, 5a-dihydrotestosterone,

testolactone, 17a-methyl-19-nortestosterone, desogestrel, dydrogesterone, ethynodiol diacetate, medroxyprogesterone, levonorgestrel, medroxyprogesterone acetate, hydroxyprogesterone caproate, norethindrone, norethindrone acetate, norethynodrel, allylestrenol, 19-nortestosterone, lynoestrenol, quingestanol acetate, medrogestone, norgestriene, dimethisterone, ethisterone, cyproterone acetate, chlormadinone acetate, megestrol acetate, norgestimate, norgestrel, desogestrel, trimegestone, gestodene, nomegestrol acetate, progesterone, 5a-pregnan-3b,20a-diol sulfate, 5a-pregnan-3b,20b-diol sulfate, 5a-pregnan-3b-ol-20-one, 16,5a-pregnen-3b-ol-20-one, 4-pregnen-20b-ol-3-one-20-sulfate, acetoxypregnenolone, anagestone acetate, cyproterone, dihydrogesterone, fluorogestone acetate, gestadene, hydroxyprogesterone acetate, hydroxymethylprogesterone, hydroxymethyl progesterone acetate, 3-ketodesogestrel, megestrol, melengestrol acetate, norethisterone, progestins and derivatives, esters, salts and mixtures thereof.

**[0156]** In an embodiment of the present invention, the active agent is a hydroxyacid. Suitable hydroxy acids include but are not limited to agaric acid, aleuritic acid, allaric acid, altraric acid, arabisaric acid, ascorbic acid, atrolactic acid, benzilic acid, citramalic acid, citric acid, dihydroxytartaric acid, erythruric acid, galactaric acid, galacturonic acid, glucaric acid, glucuronic acid, glyceric acid, glycolic acid, gularic acid, gulonic acid, hydroxypyruvic acid, idaric acid, isocitric acid, lactic acid, lyxaric acid, malic acid, mandelic acid, mannaric acid, methylactic acid, mucic acid, phenyl-lactic acid, pyruvic acid, quinic acid, ribaric acid, ribonic acid, saccharic acid, talaric acid, tartaric acid, tartronic acid, threaric acid, tropic acid, uronic acids, xylaric acid and derivatives, esters, salts and mixtures thereof.

**[0157]** In an embodiment of the present invention, the active agent is a keratolytic agent. The term "keratolytic agent" is used herein to mean a compound which loosens and removes the stratum corneum of the skin, or alters the structure of the keratin layers of skin. Keratolytic agents are used in the treatment of many dermatological disorders, which involve dry skin, hyperkeratinization (such as psoriasis), skin itching (such as xerosis), acne and rosacea. Suitable keratolytic agents include but are not limited to N-acetylcysteine, azelaic acid, cresols, dihydroxy benzene compounds, such as resorcinol and hydroquinone, alpha-hydroxy acids, such as lactic acid and glycolic acid, phenol, pyruvic acid, resorcinol, sulfur, salicylic acid, retinoic acid, isotretinoic acid, retinol, retinal, urea and derivatives, esters, salts and mixtures thereof.

**[0158]** In an embodiment of the present invention, the active agent is a lactam. Suitable lactams include but are not limited to L-galactono-1,4-lactam, L-arabino-1,5-lactam, D-fucono-1,5-lactam, D-glucaro-1,4-lactam, D-glucurono-6,3-lactam, 2,5-tri-O-acetyl-D-glucurono-6,3-lactam, 2-acetamido-2-deoxyglucono-1,5-l-actam, 2-acetamido-2-deoxygalactono-1,5-lactam, D-glucaro-1,4:6,3-dilactam-, L-idaro-1,5-lactam, 2,3,5,tri-O-acetyl-D-glucaro-1,4-lactam, 2,5-di-O-acetyl-D-glucaro-1,4:6,3-dilactam, D-glucaro-1,5-lactam methyl ester, 2-propionamide-2-deoxyglucaro-1,5-lactam and derivatives, esters, salts and mixtures thereof.

**[0159]** In an embodiment of the present invention, the active agent is a non-steroidal anti-inflammatory agent. Suitable non-steroidal anti-inflammatory agent include but are not limited to azelaic acid, oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, CP-14,304, salicylates, aspirin, dis-

alcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, acetic acid derivatives, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxeprinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, tiaprofen, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azazoprazone, trimethazone and derivatives, esters, salts and mixtures thereof.

**[0160]** In an embodiment of the present invention, the active agent is insecticide. The term "insecticide, is used herein to mean a compound which kills, inhibits the growth of, impeded the proliferation of or repels insects. Insecticides include, for example, agents that can kill lice, flees, ticks, mites, scabies and mosquitos, as well as agents that repel such insects. Suitable insecticides include but are not limited to DDT, lindane, malathion, permethrin, allethrin, biopermethrin, transpermethrin, phenothrin, diethyl-m-toluamide, dimethyl phthalate, piperonyl butoxide, pyrethroids and derivatives, esters, salts and mixtures thereof.

**[0161]** In an embodiment of the present invention, the active agent is a vasodilator. Suitable vasodilators include but are not limited to agents that modulate the activity of the enzyme nitric oxide synthase, nicotinic acid, ethyl nicotinate, amyl nitrite, amyl nitrate, ethyl nitrite, butyl nitrite, isobutyl nitrite, glyceryl trinitrate, octyl nitrite, sodium nitrite, sodium nitroprusside, clonitrate, erythryl tetranitrate, isosorbide mononitrate, isosorbide dinitrate, mannitol hexanitrate, pentaerythritol tetranitrate, penetrinitol, triethanolamine trinitrate, troInitrate phosphate (triethanolamine trinitrate diphosphate), propatylnitrate, nitrite esters of sugars, nitrite esters of polyols, nitrate esters of sugars, nitrate esters of polyols, nicorandil, apresoline, diazoxide, hydralazine, hydrochlorothiazide, minoxidil, pentaerythritol, tolazoline, scoparone, a beta-adrenergic blocker, an alpha-adrenoceptor blocker, a prostaglandin, sildenafil, dipyridamole, catecholamine, isoproterenol, furosemide, prostaglandin, prostacyclin, enalaprilat, morphine, acepromazine, prazosin ( $\alpha$ -blocker), enalapril, Captopril, amlodipine, minoxidil, tadalafil, vardenafil, phenylephrin, etilefein, caffeine, capsaicin, an extract *capsicum*, *achillea millefolium* (Yarrow), *allium sativum* (garlic), *amoracia rusticana* (horseradish), *berberis vulgaris* (barberry), *cimicifuga racemosa* (black cohosh), *coleus forskholii* (coleus), *coptis* (goldenthread), *crataegus* (hawthorn), *eleutherococcus senticosus* (siberian ginseng), *ginkgo biloba* (ginkgo), *melissa officinalis* (lemon balm), *olea europaea* (olive leaf), *panax ginseng* (Chinese ginseng), *petroselinum crispum* (parsley), *scutellaria baicalensis* (baical skullcap), *tilia europaea* (linden flower), *trigonella foenum-graecum* (fenugreek), *urtica dioica* (nettles), *valeriana officinalis* (valerian), *viburnum* (cramp, bark, black haw), *veratrum viride* (American hellebore), *verbena officinalis* (vervain), *xanthoxylum americanum* (prickly ash), *zingiber officinale* (ginger), *rauwolfia serpentina* (Indian snakeroot), *viscum album*, wild yam, sasparrilla, licorice, damiana, yucca, saw palmetto, gotu kola (*centella asiatica*), yohimbine and salts, hazel nut, brazil nut and walnut, and derivatives, esters, salts and mixtures thereof.

**[0162]** In an embodiment of the present invention, the active agent is a vasoconstrictor. Suitable vasodilators include but are not limited to ephedrine, epinephrine, phenylephrine, angiotensin, vasopressin; an extract *ephedra sinica* (ma huang), *polygonum bistorta* (bistort root), *hamamelis virgini-*

*ana* (witch hazel), *hydrastis canadensis* (goldenseal), *lycopus virginicus* (bugleweed), *aspidosperma quebracho* (*quebracho blanco*), *cytisis scoparius* (scotch broom) and cypresand and derivatives, esters, salts and mixtures thereof.

**[0163]** In an embodiment of the present invention, the active agent is a retinoid. Suitable retinoids include but are not limited to retinol, retinal, retinoic acid, all-trans retinoic acid, isotretinoin, tazarotene, adapalene, 13-cis-retinoic acid, acitretin all-trans beta carotene, alpha carotene, lycopene, 9-cis-beta-carotene, lutein and zeaxanthin.

**[0164]** In an embodiment of the present invention, the active agent is a vitamin D analog. Suitable retinoids include but are not limited to calcipotriene, cholecalciferol, 25-hydroxycholecalciferol, 1 $\alpha$ ,25-dihydroxycholecalciferol, ergocalciferol, 1 $\alpha$ ,25-dihydroxyergocalciferol, 22,23-dihydroergocalciferol, 1,24,25-trihydroxycholecalciferol, previtamin D<sub>3</sub>, tachysterol<sub>3</sub> (also termed tacalcicol), isovitamin D<sub>3</sub>, dihydrotachysterol<sub>3</sub>, (1S)-hydroxycalcicol, (24R)-hydroxycalcidiol, 25-fluorocalcicol, ercalcidiol, ertacalcicol, (5E)-isocalcicol, 22,23-dihydroercalcicol, (24S)-methylcalcicol, (5E)-(10S)-10,19-dihydroercalcicol, (24S)-ethylcalcicol and (22E)-(24R)-ethyl-22,23-didehydrocalcicol. In a preferred embodiment, the vitamin D analog is calcipotriene, which is useful in the treatment of psoriasis.

**[0165]** In an embodiment of the present invention, the active agent is selected from the group consisting of an immunosuppressants and immunoregulating agents. Suitable immunosuppressants and immunoregulating agents include but are not limited to cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod, imiquimod derivatives, esters, salts and mixtures thereof. In one or more embodiments, the immunomodulator is a calcineurin Inhibitor.

**[0166]** In an embodiment of the present invention, the active agent is a wart remover. Suitable wart removers include but are not limited to imiquimod, podophyllotoxin and derivatives, esters, salts and mixtures thereof.

**[0167]** In an embodiment of the present invention, the active agent is a photodynamic therapy (PDT) agent. Suitable PDT agents include but are not limited to modified porphyrins, chlorins, bacteriochlorins, phthalocyanines, naphthalocyanines, pheophorbides, purpurins, m-THPC, mono-L-aspartyl chlorin e6, bacteriochlorins, phthalocyanines, benzoporphyrin derivatives, as well as photosensitiser precursors, such as aminolevulinic acid and derivatives, esters, salts and mixtures thereof.

**[0168]** In an embodiment of the present invention, the active agent is an antioxidant or a radical scavenger. Suitable antioxidants and radical scavengers agents include but are not limited to ascorbic acid, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopheryl sorbate, tocopheryl acetate, butylated hydroxy benzoic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid, propyl gallate, uric acid, sorbic acid, lipoic acid, diethylhydroxylamine, amino-guanidine, glutathione, dihydroxy fumaric acid, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and polyunsaturated oils, containing omega-3 and omega-6 fatty acids (e.g., linoleic and linolenic acid, gamma-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid and derivatives, esters, salts and mixtures thereof.

**[0169]** In an embodiment of the present invention, the active agent is a self-tanning agent, such as dihydroxyacetone.

**[0170]** In an embodiment of the present invention, the active agent is an agent, capable of treating hyperhidrosis. Suitable hyperhidrosis agents include but are not limited to anticholinergic drugs, boric acid, tannic acid, resorcinol, potassium permanganate, formaldehyde, glutaraldehyde, methenamine, a Lewis acid, aluminum chloride, aluminum chlorohydrates, zirconium chlorohydrates, aluminum-zirconium-Glycine (AZG) complex, aluminum hydroxybromide, a glycopyrrolate compound, a 5-alpha-reductase inhibitor, finasteride, epristeride, flutamide, spironolactone, saw palmetto extract, cholestan-3-one, a mono- and dicarboxylic acid having 4 to 18 carbon atoms, botulinum toxin, a 5-HT<sub>2C</sub> receptor antagonist, a 5-HT<sub>2C</sub> receptor antagonist, ketanserine, ritanserine, mianserine, mesulergine, cyproheptadine, fluoxetine, mirtazapine, olanzapine and ziprasidone.

**[0171]** In an embodiment of the present invention, the active agent is a sunscreen agent. Suitable sunscreen agents include but are not limited to titanium dioxide, zinc oxide, zirconium oxide, iron oxide, p-aminobenzoic acid and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilic acid derivatives (i.e., o-aminobenzoates, methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, a-phenyl cinnamitrile; butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxycinnamic acid derivatives (esculetin, methylsculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); dihydroxynaphthoic acid, o- and p-hydroxybiphenyldisulfonates, coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl), diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, quinone salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carboto) (6-propyl piperonyl)ether; hydroquinone; benzophenones (oxybenzene, sulisobenzone, dioxybenzene, benzo-resorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; octocrylene; [3-(4'-methylbenzylidene bornan-2-one), terephthalylidene dicamphor sulfonic acid and 4-isopropyl-di-benzoylmethane.

**[0172]** In an embodiment of the present invention, the active agent is a figure-forming agent and an agent, capable of treating cellulite. Suitable such agents include but are not limited to baldderwack extract, butcher's, broom, cayenne, dandelion, red clover, *ginkgo biloba*, horse chestnut, witch hazel and borage oil, caffeic acid, nicotinic acid, theophylline and pentoxyphilline and salts and derivatives thereof.

**[0173]** Several disorders of the skin, body cavity or mucosal surface (e.g., the mucosa or the cavity of the nose, mouth, eye, ear, vagina or rectum) involve a combination of etiological factors. For example, fungal and bacterial infections and that are inflamed and have symptoms of redness and/or itching warrant therapy that combines an anti-infective agent and an anti-inflammatory agent. Thus, in several cases, combining at least two active agents that treat different etio-

logical factors results in a synergistic effect and consequently higher success rate of the treatment.

In certain cases, the composition contains two active agents, where each of the active agents require a different pH environment in order to remain stable. For example, corticosteroids are typically stable at acidic pH values (they have a maximum stability at a pH of about 4-6) and of vitamin D analogues are typically stable at basic pH values (they have a maximum stability at pH values above about 8). In order to circumvent the problem of instability it is preferred that the composition is substantially non-aqueous. The term "substantially non-aqueous" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%.

#### Fields of Applications

**[0174]** The foamable carrier of the present invention is suitable for treating any infected surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

**[0175]** By selecting a suitable active agent, or a combination of at least two active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having 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, paronychia 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, granuloma 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, moniliiasis, 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.

**[0176]** Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include 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.

**[0177]** In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

**[0178]** In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn. This use is particularly important since the composition of the present invention creates a thin, semi-occlusive layer, which coats the damaged tissue, while allowing exudates to be released from the tissue.

**[0179]** The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

**[0180]** In light of the hygroscopic nature of the composition, 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 appropriate protective agents, the foam is suitable for the treatment or prevention of post surgical adhesions. The use of foam is particularly advantageous because foam can expand in the body cavity and penetrate into hidden areas that cannot be reached by any other alternative means of administration.

**[0181]** 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.

#### Example 1

##### Foamable Carriers Containing Polyols

**[0182]**

Ingredient	TECH		
	TECH PG-014 % W/W	TECH PG-015 % W/W	PG-016 % W/W
Propylene glycol (PG)	82.00	92.00	60.00
Laureth-4	2.00	2.00	2.00

-continued

Ingredient	TECH		
	TECH PG-014 % W/W	TECH PG-015 % W/W	PG-016 % W/W
Glyceryl stearate and PEG-100 stearate (Simulsol 165)	4.00	4.00	3.00
PEG 4000	10.00		
Glycerin anhydrous			33.00
Hydroxypropylcellulose (Klucel EF)	2.00	2.00	2.00
Total	100.00	100.00	100.00
Foam quality	Good	Good	Good
Shakability	Shakable	Shakable	Shakable

Notes:

The compositions are substantially non-aqueous

Composition TECH PG-015 contains the minimum number of components that constitute a foamable composition, which upon release from an aerosol pressurized container affords foam of Good or Excellent quality. It contains a diol (PG), a polymeric agent (Klucel EF), and a non-ionic surface active agent (PEG-100 stearate and Laureth 4)

Composition TECH PG-014 demonstrates that the addition of 10% PEG (secondary polar solvent) maintains Good foam quality.

Composition TECH PG-016 demonstrates that a mixture of two polyols (PG and glycerin) maintains Good foam quality. This composition possesses high skin hydration effect.

The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

#### Example 2

##### Foamable Carriers Containing Polyols

**[0183]**

Ingredient	TECH		
	PG-021 % W/W	PG-024 % W/W	PG-025 % W/W
Propylene glycol (PG)	91.00	58.00	43.00
Stearyl alcohol	2.00	1.00	1.00
Laureth-4	2.00	2.00	2.00
Glyceryl stearate and PEG-100 stearate (Simulsol 165)	3.00	3.00	3.00
Glycerin		33.00	33.00
Hydroxypropylcellulose (Klucel EF)	2.00	3.00	3.00
Dimethyl isosorbide (DMI)			15.00
Total	100.00	100.00	100.00
Foam quality	Excellent	Excellent	Excellent
Shakability	Shakable	Shakable	Shakable

Notes:

Composition TECH PG-021, 24 and 25 demonstrates that the addition of 1-2% stearyl alcohol (foam adjuvant) facilitates the formation of foam with Excellent quality. Substituting Stearyl alcohol with stearic acid results in an excellent foam too.

Composition TECH PG-025 demonstrates that the addition of 15% DMI (foam adjuvant) facilitates the formation of foam with Excellent quality. This composition possesses high skin penetration enhancing properties.

The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

**[0184]** The following procedure was employed when the compositions of Example 2 were produced.

##### Step 1: Preparation of Phase A

**[0185]** 1. Heat Propylene glycol and stearyl alcohol to 80-85° C.

**[0186]** 2. Add Klucel while mixing.

**[0187]** 3. Cool to 70-75° C. Add all other ingredients while mixing. Agitation continues until solution uniformity is reached

**[0188]** 4. Cool solution to 30° C. with moderate mixing.



## Step 2: Canisters Filling and Crimping

**[0189]** 1. Each aerosol canister 35×70 mm is filled with 30±5% g of the composition

**[0190]** 2. Each canister was closed with an aerosol valve, using a vacuum crimping machine.

## Step 3: Pressurizing

**[0191]** Propellant (mix of propane, butane and isobutane) was added to each of the canisters

## Example 3

## Foamable Carriers Containing Polyols

**[0192]**

Ingredient	TECH	TECH	TECH
	PG-026 % W/W	PG-027 % W/W	PG-028 % W/W
Stearyl alcohol	2.00	1.00	1.00
Propylene glycol (PG)	76.00	46.00	78.00
Laureth-4	2.00	2.00	2.00
Glyceryl stearate (and) PEG-100 stearate (Simulsol 165)		1.50	
Glycerin anhydrous		33.00	
Hydroxypropylcellulose (Klucel EF)	2.00	1.50	1.50
Dimethyl isosorbide (DMI)	15.00	15.00	15.00
Glyceryl stearate	1.00		1.00
Ceteareth-6 (and) stearyl alcohol (Macrogol cetostearyl ether)	2.00		1.50
Total	100.00	100.00	100.00
Foam quality	Excellent	Excellent	Excellent

## Notes:

Composition TECH PG-027 demonstrates that a mixture of two polyols (PG and glycerin, plus DMI (secondary polar solvent) maintains Excellent foam quality. This composition possesses high skin hydration effect. It further possesses high skin penetration enhancing properties.

The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

## Example 4

Additional Foamable Carriers Containing Polyols,  
Having Excellent Foam Structure

**[0193]**

Ingredient	TECH-	TECH-	TECH-	TECH-	TECH-
	PG 029 % w/w	PG 030 % w/w	PG 031 % w/w	PG 032 % w/w	PG 033 % w/w
Propylene Glycol	91.0	58.0	43.0	46.0	78.0
Stearyl Alcohol	2.0	1.0	1.0	1.0	1.0
Glycerin	—	33.0	33.0	33.0	—
Klucel EF	2.0	3.0	3.0	1.5	1.5
Laureth-4	2.0	2.0	2.0	2.0	2.0
Simulsol 165	3.0	3.0	3.0	1.5	—
Dimethyl Isosorbide	—	—	15.0	15.0	15.0
Macrogol Cetostearyl Ether	—	—	—	—	1.5
Glyceryl Stearate	—	—	—	—	1.0

## Example 5

Foamable Polyols Compositions, Containing Steroid  
Drugs

**[0194]** The following steroids were included in formulations were included in formulations TECH 30, 31 and 33: bethamethasone valerate 0.12%, clobetasol propionate 0.05%, bethamethasone dipropionate 0.05%, fluocinolone acetonide 0.025%, hydrocortison acetate 0.5% and hydrocortison butyrate 0.1%. All samples were stored at 50° C. for 4 weeks, in order to assess their stability. The following table provides the results of this short-term stability study, which indicated high compatibility between the polyol composition and the steroid drugs, which are known to be temperature-sensitive.

	% Degradation after 4 weeks at 50° C.	
	TECH-PG 032	TECH-PG 033
Bethamethasone Valerate 0.12%	1.8%	1.7%
Clobetasol Propionate 0.05%	4.2%	5.0%
Bethamethasone Dipropionate 0.05%	0	0
Fluocinolone Acetonide 0.025%	1.3%	1.7%
Hydrocortison Acetate 0.5%	1.6%	2.1%
Hydrocortison Butyrate 0.1%	2.6%	2.8

## Example 6

Foamable Polyol Pharmaceutical Composition  
Comprising a Combination of Betamethasone  
Dipropionate and Calcipotriol

**[0195]**

Ingredient	FXCLB1	FXCLB2
	% W/W	% W/W
Propylene glycol	90.945	77.945
Stearyl alcohol	2.00	1.00
Klucel EF	2.00	1.50
Laureth-4	2.00	2.00
Simulsol 165	3.00	
Macrogol Cetostearyl Ether		1.50
Glyceryl Stearate		1.00
Dimethyl isosorbide		15.00
Calcipotriol	0.005	0.005
Betamethasone Dipropionate	0.05	0.05

## Notes:

Composition FXCLB1 and FXCLB2 contain two active agents (a corticosteroid and a vitamin D derivative, which are known to exert a synergistic therapeutic effect in psoriasis. These compositions contribute to enhanced skin penetration of the active agents. The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

Example 7

Foamable Polyol Pharmaceutical Composition  
Comprising Acyclovir

[0196]

Ingredient	% W/W
Acyclovir	5.00
Propylene Glycol	43.70
Stearyl Alcohol	0.95
Glycerin	31.35
Hydroxypropyl cellulose	1.43
Laureth-4	1.90
Glyceryl Monostearate/PEG 100 Stearate	1.43
Dimethyl Isosorbide	14.25

Notes:

The composition contains acyclovir, which is not fully soluble in the polyol and DMI mixture. However, due to the unique composition, the acyclovir does not readily precipitate and does not undergo caking. Furthermore, thanks to the low viscosity of the composition, upon shaking the active agent readily re-disperses in the composition, resulting in full formulation uniformity. The combination of polyols and dimethyl isosorbide contributes to enhanced skin bioavailability of the active agent. The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

Example 8

Foamable Compositions Containing Polyethylene  
Glycol

[0197]

	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
PEG400	87.50	91.50	87.50	89.50	87.50	87.50	87.50
Klucel MX (hydroxypropyl cellulose)	0.50	0	0.50	0	0.50	0	0.50
Klucel LF (hydroxypropyl cellulose)	0	0.50	0	0.50	0	0.50	0
Lipocol C2 (POE (2) cetyl ether)	2.00	2.00	0	0	0	0	0
Myrj 52	0	0	2.00	2.00	0	0	0
Steareth-2	0	0	0	0	2.00	2.00	0
Dermofeel G10L (Polyglyceryl-10 Laurate)	0	0	0	0	0	0	2.00
Propellant	10	6	10	8	10	10	10
Density	0.060	0.063	0.063	0.055	0.052	0.050	0.075

Notes:

The liquefied or gas propellant can be added at a concentration of about 3% to about 25%. The foams of this example have a non-ionic surface active agent at a concentration of 2%. Total amounts of surface active agent foam adjuvant and polymeric agent is in the range of 2.5%. The compositions are useful as carriers of various active therapeutic active agents.

Example 9

Foamable Hygroscopic Compositions, Containing  
Mupirocin

[0198] The following table exemplifies the use of PEG as a hygroscopic substance, which also serves as an effective solvent for Mupirocin, which is practically insoluble in mineral oil and other commonly used ointment solvents. Note that Mupirocin is incompatible with most solvents and thus, a foam comprising PEG as the sole solvent is highly valuable.

	% w/w	% w/w	% w/w
Mupirocin	2.00	2.00	2.00
PEG400	89.50	89.50	89.50
Hydroxypropyl cellulose	0.50	0.50	0.50
Steareth-2	2.00	1.00	0

-continued

	% w/w	% w/w	% w/w
Polyglyceryl-10 Laurate			2.00
Propellant (Propane/butane)*	6.0	6.0	6.0
Density	0.060	0.060	0.062

Notes:

The liquefied or gas propellant can be added at a concentration of about 3% to about 25%. The foams of this example have a non-ionic surface active agent at a concentration of 2%. Total amounts of surface active agent foam adjuvant and polymeric agent is in the range of 2.5% (w/w).

Example 10

Foamable Hygroscopic Compositions, Containing  
Terbinafine

[0199] The following table exemplifies the use of PEG as a hygroscopic substance, which also serves as an effective solvent for terbinafine, which is hard to dissolve in common formulation excipients.

	% w/w	% w/w	% w/w
Terbinafine	2.00	2.00	6.00
PEG400	89.50	89.50	89.50
Hydroxypropyl cellulose	0.50	0.50	0.50
Steareth-2	2.00	1.00	0

-continued

	% w/w	% w/w	% w/w
Polyglyceryl-10 Laurate			2.00
Propellant (Propane/butane)*	6.0	6.0	6.0
Density	0.060	0.060	0.062

Example 11

Comparative In-Vitro Activity of a Hygroscopic  
Composition Containing Terbinafine

[0200] A comparative in-vitro study was set to evaluate the effect of Composition A, consisting of 2% terbinafine, 95.3% gr. polyethylene glycol, 0.5% hydroxypropyl cellulose and

2.2% steareth-2, in comparison with Composition B (an oil in water emulsion containing 2% terbinafine) and Composition C a commercial 1% bifonazole cream.

[0201] Three fungal strains (*microsporum canis*, *trichophyton mentagrophytes* and *trichophyton rubrum*) and one yeast (*candida albicans*) were seeded in the center of a Petri dish, and then, were surrounded by a film containing each of the compositions, using a swab, soaked with each of the compositions. The proliferation and spreading of the microorganisms was followed up for 14 day by visual and photographic observations.

[0202] As shown in FIG. 1, Composition A inhibited the proliferation and spreading of all the fungal and yeast strains effectively. By contrast, both Compositions B and C failed to inhibit the growth of candida. Composition C was also ineffective in the inhibition of *microsporum canis* and *Trichophyton rubrum*.

Example 12

Foamable Hygroscopic Composition Containing Dimethyl Isosorbide

[0203]

	% w/w	% w/w	% w/w	% w/w
Oleyl alcohol	2.50	—	—	—
IPM	5.00	5.00	5.00	—
Caprylic/Capric Triglyceride (MCT oil)	5.00	5.00	5.00	46.00
Epikuron P100	—	—	—	10.00
PPG-15 stearyl ether	—	—	—	2.00
Sorbitane stearate	8.00	8.00	8.00	2.00
Glyceril monostearate	—	1.00	1.00	1.00
Stearyl alcohol	—	5.00	5.00	—
Cetostearyl alcohol	8.00	—	—	—
Klucel MF	—	0.50	—	—
PVP K-90	—	—	—	0.50
Sistema SP50	5.00	8.00	8.00	—
Propylene glycol	2.50	—	—	—
DMI	55.50	59.00	59.50	20.00
Water pure	—	—	—	10.00
Phenonip	0.50	0.50	0.50	0.50
Propellant	8.00	8.00	8.00	8.00

Example 13

Hygroscopic Antifungal Compositions

[0204]

	Ointment Type			Lacquer Type		
	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
PEG 400	92.00	92.00	93.00	—	54.00	46.00
PEG 4000	6.00	—	—	—	—	—
PEG 6000	—	6.00	6.00	—	10.00	8.00
Ethyl acetate/ Isopropanol	—	—	—	30.00	30.00	30.00
Urea	—	—	—	—	—	10.00
Terbinafine	2.00	2.00	—	2.00	4.00	—
Ciclopirox	—	—	1.00	—	—	4.00

[0205] The lacquer type compositions are suitable for the treatment of infected cornified tissues, and particularly the nail.

Example 14

Comparison Between Polyethylene-Based Foamable Compositions with and without Gelling Agent

[0206] The compositions of the test articles are provided in the following table. All foams were dispensed on a warm surface (38° C.), and the time to full collapse of the foam was measured. As shown in the table, it has been strikingly demonstrated that foam compositions without a gelling agent exhibit a 100% breakdown within 30 seconds, while foams containing gelling agent remained, with and without surfactant, were stable for several minutes. This is relevant from the usability point of view, since a foam that is unstable at skin temperature cannot be applied to large areas effectively.

	Formulations without gelling agent				Formulation with gelling agent	
	PG33 % w/w	PG34 % w/w	PG35 % w/w	PG36 % w/w	TEC49 % w/w	PG29 % w/w
PEG 400	87.25	93.00	91.00	92.00	90.50	93.50
Klucel GF (gelling agent)	—	—	—	—	0.50	0.50
Cetareth-15 Emulsifying Wax NF	—	—	2.00	1.00	—	—
Steareth-10	—	0.40	—	0.50	—	—
PEG-40 stearate	1.35	—	—	—	—	—
Steareth-2	—	0.60	1.00	0.50	1.00	—
Span 60	2.70	—	—	—	—	—
Polysorbate 60	0.90	—	—	—	—	—
Propellant	6.00	6.00	6.00	6.00	8.00	6.00
Collapse time (Seconds; 38° C.)	<30	<30	<30	<30	240	>300

Example 15

Foamable Hygroscopic Composition Containing Polyethylene Glycol with No Surfactant

[0207]

	% w/w
PEG 400	93.50
Klucel GF	0.50
Propellant (Butane/propane)	6.00
Foam quality	E
Density	0.09

1. A method of treating a disorder of the skin, body cavity, or mucosal surface, the method comprising applying a therapeutically effective amount of a foamable hygroscopic pharmaceutical composition to the skin, body cavity, or mucosal surface of a patient in need thereof, wherein the foamable hygroscopic pharmaceutical composition comprises:

- i) a carrier composition comprising:
  - a) a therapeutically effective amount of one or more active agents;
  - b) about 50% to about 98% by weight of the carrier composition of a polar solvent selected from the group consisting of a polyol, a polyethylene glycol (PEG), or a mixture thereof;

- c) 0% to about 48% by weight of the carrier composition of a secondary polar solvent;
- d) about 0.01% to about 5% by weight of the carrier composition of a gelling agent; and
- e) 0% to about 25% by weight of the carrier composition of water; and

ii) a liquefied or compressed gas propellant; wherein the foamable hygroscopic pharmaceutical composition forms a breakable foam upon release from a pressurized container; wherein the breakable foam does not immediately collapse upon exposure to skin temperature; and wherein the breakable foam breaks under shear force.

2. The method of claim 1, wherein the gelling agent comprises a cellulose polymer.

3. The method of claim 1, wherein the polar solvent is a PEG, and the PEG is selected from the group consisting of PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 4000, PEG 6000, and PEG 8000.

4. The method of claim 1, wherein the foamable hygroscopic pharmaceutical composition does not contain a surface-active agent.

5. The method of claim 1, wherein the polar solvent is a polyol, and the polyol comprises at least one of glycerin, butane-1,2,3-triol, butane-1,2,4-triol, hexane-1,2,6-triol, propylene glycol, butanediol, butenediol, butynediol, pentanediol, hexanediol, octanediol, neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol, and dibutylene glycol, or a mixture of at least two polyols.

6. The method of claim 1, wherein the polar solvent comprises a mixture of at least one polyol and at least one PEG.

7. The method of claim 1, wherein the foamable hygroscopic pharmaceutical composition is substantially non-aqueous.

8. The method of claim 1, wherein the foamable hygroscopic pharmaceutical composition is substantially free of short-chain alcohols.

9. The method of claim 1, wherein the foamable hygroscopic pharmaceutical composition forms a stable foam at normal skin temperature for at least about 240 seconds upon release from the pressurized container.

10. The method of claim 1, wherein the carrier composition further comprises about 0.2% to about 5% by weight of the carrier composition of a surface-active agent.

11. The method of claim 10, wherein the surface-active agent comprises a non-ionic surfactant.

12. The method of claim 10, wherein the surface-active agent comprises at least one non-ionic surfactant and at least one ionic surfactant.

13. The method of claim 10, wherein the carrier composition further comprises a hygroscopic substance selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sugar alcohols, honey, and a PEG containing surfactant; and wherein the carrier composition has an Aw value of less than 0.9.

14. The method of claim 1, wherein the disorder is selected from the group consisting of 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, fungal infection of nail and nail bed, infection of mucosa, 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, paronychia 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, granuloma 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, 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; and wherein the active agent is suitable for treating the disorder.

15. The method of claim 1, wherein the active agent is selected from the group consisting of alclometasone dipropionate, amcinafel, amcinafide, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone dexamethasone-phosphate, dipropionate, betamethasone valerate, budesonide, chlorprednisone, chlorprednisone acetate, clescinolone, clobetasol, clobetasol propionate, clobetasol valerate, clobetasone, clobetasone butyrate, clocortelone, cortisone, cortodoxone, craposone butyrate, desonide, desoxymethasone, dexamethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, difluorone diacetate, diflurprednate, fludrenolone, flucetonide, flucoronide, flucorolone acetonide, flucortine butylesters, fludroxycortide, fludrocortisone, flumethasone, flumethasone pivalate, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluosinolone acetonide, fluperolone, fluprednidene acetate, fluprednisolone hydrocortamate, fluradrenolone, fluradrenolone acetonide, flurandrenolone, fluticasone, halcinonide, halobetasol, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cyclopentylpropionate, hydrocortisone valerate, hydroxyltri-aminolone, medrysone, meprednisone, alpha-methyl dexamethasone, methylprednisolone, methylprednisolone acetate, mometasone furoate, paramethasone, prednisolone, prednisone, pregnenolone, progesterone, spironolactone, triameinolone, triameinolone acetonide, and salts thereof.

16. The method of claim 1, wherein the active agent is an anti-infective agent and the anti-infective agent is selected from one or more of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent, and an antiparasitic agent.

**17.** The method of claim **16**, wherein the anti-infective agent is an antifungal agent and the antifungal agent is selected from the group consisting of a polyene, natamycin, nystatin; an allylamine, naflifine, terbinafine; an imidazole, bifonazole, clotrimazole, econazole, fenticonazole, ketoconazole, miconazole, oxiconazole; a diazole, a triazoles, fluconazole, itraconazole, terconazole, tolnaftate, ciclopirox, undecylenic acid, sulbentine, griseofulvin, Amphotericin B, flucytosine (5FC), a morpholine compound, amorolfine, and salts thereof.

**18.** The method of claim **16**, wherein the anti-infective agent is an antibacterial agent and the antibacterial agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, metronidazole, an antibiotic glycopeptide, a macrolide, erythromycin, clindamycin, an antibiotic nucleoside, an antibiotic peptide, polymyxin B, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, fucidic acid, mupirocin, chloramphenicol, a sulfonamide, tetracycline, an antibiotic metal, silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium, an oxidizing agent, iodine, iodate, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, chlo-

rohexidine, a triguanide, a bisbiguanide, a polymeric biguanide, a naturally occurring antibiotic compound, and salts thereof.

**19.** The method of claim **16**, wherein the active agent comprises a combination of (1) a corticosteroid; and (2) and active agent selected from the group consisting of an anti-infective agent, an antifungal agent, an antimicrobial agent, an antiviral agent, an anti-acne agent, a retinoid, a vitamin D3, calcipotriol, and antipsoriasis agent, a keratolytic agent, an anti-proliferative agent, an anti-cancer agent, a non-steroidal anti-inflammatory agent, an immunomodulator, an immunosuppressant, and an anti-rosacea agent.

**20.** The method of claim **1**, wherein the active agent comprises a combination of (1) a keratolytic agent; and (2) and active agent selected from the group consisting of a corticosteroid, an anti-infective agent, an antifungal agent, an antimicrobial agent, an antiviral agent, an anti-acne agent, a retinoid, a vitamin D3, calcipotriol, and antipsoriasis agent, an anti-proliferative agent, an anti-cancer agent, a non-steroidal anti-inflammatory agent, an immunomodulator, an immunosuppressant, and an anti-rosacea agent.

**21.** The method of claim **17**, wherein the active agent is terbinafine and the disorder is a fungal infection, a yeast infection, or both.

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