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(54) Title: OLEAGINOUS PHARMACEUTICAL AND COSMETIC FOAM

(57) Abstract: The invention 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 composition includes at least one solvent selected from the group consisting of: 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.



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## **OLEAGINOUS PHARMACEUTICAL AND COSMETIC FOAM**

### **FIELD OF THE INVENTION**

**[0001]** The invention relates to oleaginous foam compositions including cosmetic or therapeutic active agents, and methods of topical treatment using the compositions.

### **BACKGROUND OF THE INVENTION**

**[0002]** Certain foam products for topical application of therapeutical agents and cosmetics have been prepared as oil-in-water emulsions. Foams and, in particular, foam compositions having a high oil content are complicated systems that do not form under all circumstances. Slight shifts in foam composition, such as the addition of an active ingredient, may destabilize the foam. It is known in the art that hydrophobic solvents are difficult to formulate into a foam-producing product. Addition of conventional hydrophobic solvents interferes with the foam forming ability of the surface active agent, and thus, in the few foam products containing high-oil concentrations that have been reported, high surface active agent concentrations are used, which may cause undesirable irritation on one hand, and costly raw material usage on the other hand are used.

**[0003]** Oleaginous formulations for the preparation of cosmetic and therapeutic compositions are known in the art.

**[0004]** US Pat. No. 6,620,773 relates to a foaming oil composition, including a surface active agent mixture and an oil component, the surface active agent mixture containing an anionic or zwitterionic surface active agent, a nonionic surface active agent and at least one ethoxylated alkyl phosphate ester component. The surface active agent mixture ranges from about 15% to about 50% of the total composition, and that of the oil component ranges from about 50% to about 85%.

**[0005]** US Pat. Nos. 5,700,396 and 5,589,515 disclose a cosmetic emulsion composition containing 0.1 to 99 wt% oily component (balance aqueous component). The oily component includes at least 85% weight % of cis  $\Delta^9$ -octadecanoic acid or derivatives thereof, which cis  $\Delta^9$ -octadecanoic acid or derivatives thereof serve as a surface active agent in the formulation.

**[0006]** US Pat. No. 6,524,594 describes a gelled oil composition containing an emulsifier, a gelling agent, an oil, and a surface active agent for producing a significant

amount of foam when applied to the skin in the presence of water. The surface active agent is used in an amount from about 10% to about 20%, and more preferably, from about 15% to about 20%.

**[0007]** US Pat. No. 6,121,210 discloses foamable, silicone oil compositions and methods of lubricating surfaces with such compositions. The compositions are oil-in-water emulsions comprising silicone oil-in-water emulsion, a liquid propellant and a foam builder comprising a solid, non-ionic lipophilic surface active agent having an HLB value of about 3 to about 8. Foam stabilizers including long chain fatty alcohols are included. A propellant is included to create a foamable composition.

**[0008]** 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).

**[0009]** In general, the foamable compositions of the art are based on oil-in-water emulsions. Furthermore, they often include a high content level of surface active agents and foaming agents required to form acceptable stable and possess low specific gravity foams. Such surface active agents, and particularly ionic surface active agents, such as anionic surface active agents (e.g. sodium lauryl sulfate (SDS)), may have adverse effects on certain patients, including concentration-dependent skin irritation.

**[0010]** There remains an unmet need for improved, stable and non-irritating oleaginous foam formulations, intended for dermal and mucosal delivery of pharmaceutical and cosmetic, with unique therapeutic and cosmetic properties.

## SUMMARY OF THE INVENTION

**[0011]** The present invention provides stable, oleaginous foam-forming compositions including at least one active agent for dermal and mucosal delivery. The composition is dispensed as a foam providing a stable product that is pleasant and easy to spread, resulting in high patient compliance. The "oleaginous" composition has the organoleptic character of an oily substance, i.e., an oily feeling, when topically administered to the skin or mucosal tissue.

**[0012]** According to one aspect of the present invention, the composition includes:

- a. a solvent selected from the group consisting of a hydrophobic solvent, 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;
- b. a surface-active agent at a concentration of about 0.1% to about 10% by weight of the total composition;
- c. optionally, a gelling agent at a concentration of about 0.1% to about 5% by weight of the total composition;
- d. an active agent in a therapeutically effective concentration; and
- e. a propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0013]** Water and optional ingredients are added to complete the total weight to 100%, although the composition may be essentially free of lower alkyl alcohols. In one or more embodiments, the oleaginous composition of the present invention contains less than about 5% of a short chain alcohol having up to 5 carbon atoms in its carbon chain skeleton.

**[0014]** In one or more embodiments, the oleaginous composition includes water at a concentration less than about 30%, preferably less than about 20%, more preferably less than about 10% by weight.

**[0015]** In one or more embodiments, the oleaginous composition of the present invention further includes a foam adjuvant.

**[0016]** In yet other embodiments, the oleaginous composition of the present invention forms a water in oil emulsion.

**[0017]** In one or more embodiments, the oleaginous composition of the present invention includes a hydrophobic solvent having solubility in distilled water at ambient temperature of less than about one gram per 100 ml. The hydrophobic solvent may be a mineral oil, MCT oil, triglyceride oil, silicone oil, a polyunsaturated oil, an unsaturated oil and an essential oil, and mixtures thereof.

**[0018]** In one or more embodiments, the oleaginous composition includes a co-solvent. In one or more embodiments, the co-solvent is a polyol. In one or more embodiments, the co-solvent is polyethylene glycol derivative, or glycerin. In one or more embodiments, the oleaginous composition of the present invention includes a

mixture of at least one hydrophobic solvent and at least one co-solvent. The mixture of at least one hydrophobic solvent and the at least one co-solvent may have a weight ratio of about 1:8 to about 8:1. In one or more embodiments, a mixture of at least one hydrophobic solvent and glycerin is used; and the mixture may have a weight ratio of about 1:4 to about 4:1, or about 1:2 to about 2:1.

**[0019]** According to one or more embodiments, the oleaginous composition includes at least one solvent having a high solubilization capacity, termed herein a "potent solvent". In the context of the present invention, a potent solvent is a solvent other than mineral oil and solubilizes a specific active agent substantially better than a hydrocarbon solvent such as mineral oil or petrolatum, for example, 5-fold better than mineral oil or 10-fold better than mineral oil.

**[0020]** In one or more embodiments, the oleaginous composition of the present invention contains a potent solvent selected from the group consisting of a polyol, polyethylene glycol, propylene glycol, hexylene glycol, butanediols and isomers thereof, glycerol, benzyl alcohol, dimethyl sulfoxide (DMSO), ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, dimethyl isosorbide, glycofurool and ethoxydiglycol (transcutol) and mixtures thereof in any proportion.

**[0021]** In one or more embodiments, the oleaginous composition includes at least one gelling agent selected from the group consisting of natural polymeric materials, semi-synthetic polymeric materials, synthetic polymeric materials, inorganic gelling agents and mixtures thereof. Yet, in additional embodiments, a gelling agent is not essential.

**[0022]** The oleaginous composition of the present invention upon extrusion from a pressured container has a specific gravity of about 0.02 gr/ml to about 0.5 gr/mL, and is useful for treating, alleviating or preventing a dermatological or mucosal disorder.

**[0023]** According to a further aspect of the present invention, an oleaginous water-in-oil emulsion is provided. The emulsion can be essentially free of short chain alcohols. The emulsion includes:

- a. at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent and an emollient at a concentration of about 30% to about 96.5% by weight;
- b. water;
- c. at least one non-ionic lipophilic surface acting agent having an HLB value of

about 3 to about 10 at a concentration of about 0.1 % to less than about 10% by weight;  
d. optionally, at least one gelling agent at a concentration of about 0.1% to about 5% by weight.

e. at least one active agent at a therapeutically effective concentration; and

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

**[0024]** In one or more embodiments, the oleaginous water-in-oil emulsion contains less than about 5% of a short chain alcohol having up to 5 carbon atoms in its carbon chain skeleton. In another embodiment the oleaginous composition further includes a foam adjuvant.

**[0025]** In one or more embodiments, the oleaginous water-in-oil emulsion contains a hydrophobic solvent and water at a weight ratio of about 1:3 to about 6:1.

**[0026]** In one or more embodiments, the oleaginous water-in-oil emulsion contains a hydrophobic solvent having solubility in distilled water at ambient temperature of less than about one gram per 100 ml. The hydrophobic solvent may be selected from mineral oil, MCT oil, triglyceride oil, silicone oil, a polyunsaturated oil, an unsaturated oil and an essential oil.

**[0027]** The oleaginous water-in-oil emulsion may include a potent solvent selected from the group consisting of a hydrophobic solvent other than mineral oil, a co-solvent and an emollient, wherein the potent solvent solubilizes the active agent substantially better than mineral oil solubilizes the active agent, e.g at least 5-fold better or at least 10-fold better than mineral oil solubilizes the active agent.

**[0028]** In one or more embodiments, the oleaginous water-in-oil emulsion contains a surface-active agent having an HLB value in the range of about 3 to about 10, for promoting the formation of a water-in-oil emulsion.

**[0029]** In one or more embodiments, the oleaginous water-in-oil emulsions contains at least one gelling agent selected from the group consisting of natural polymeric materials, semi-synthetic polymeric materials, synthetic polymeric materials, inorganic gelling agents and mixtures thereof. Yet, in additional embodiments, a gelling agent is not essential.

**[0030]** The active agent can be a therapeutic agent or a cosmetic agent. The therapeutic agent is selected for the treatment or prophylaxis of a disorder of the skin, mucosal membrane, ear channel, vagina, penile urethra and rectum. In one embodiment therapeutic agent is selected from the group consisting of an anti-infective,

an antibiotic, an antibacterial agent, an antifungal agent, an antiviral agent, an antiparasitic agent, an antiinflammatory agent, an anesthetic, an analgesic, an antiallergic agent, a corticosteroid, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, a lubricating agent and mixtures thereof.

**[0031]** Alternatively, the active agent is an inorganic solid matter, preferably a metal oxide, more preferably titanium oxide and zinc oxide.

**[0032]** The active agent can also be a cosmetic agent such as a retinoid, an anti-wrinkle agent, a radical scavenger, a self-tanning agent, a skin whitening agent a skin protective agent, an anti-cellulite agent, a massaging oil and an anti-wart agent.

**[0033]** In another aspect, the present invention provides a method of treating, alleviating or preventing a dermatological or mucosal disease or disorder by administering topically to a subject having the disease or disorder a therapeutically effective amount of the oleaginous compositions or the oleaginous water-in-oil emulsions of the present invention.

**[0034]** In yet another aspect, the present invention also provides a method of designing a foamable composition, containing at least one active agent that is substantially insoluble in a hydrocarbon solvent including mineral oil. The method includes selecting at least one active agent, and identifying a solvent that solubilizes the active agent substantially better than mineral oil solubilizes the active agent. The method may further include the step of adjusting the type and concentration of surface active agent and gelling agent to provide a foamable composition.

**[0035]** In one or more embodiments, the potent solvent solubilizes the active agent 5-fold better or even 10-fold better than mineral oil solubilizes the active agent.

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

**[0036]** Despite the commonly known fact that hydrophobic solvents, and oils in particular, are difficult to formulate into foam-producing products and that addition of conventional hydrophobic solvents interferes with the foam forming ability of the surface active agent, the present invention has surprisingly discovered stable oleaginous foam compositions. The oleaginous compositions may include at least one active agent for dermal, transdermal and mucosal delivery. The oleaginous compositions are dispensed as a foam providing a stable product that is pleasant and easy to use for high patient and consumer compliance. The at least one active agent may be a therapeutically active agent or a cosmetic agent.

**[0037]** The term "oleaginous" is defined as "having the nature or qualities of oil". The terms "oleaginous composition", "oleaginous foam", "oleaginous emulsion" and "oleaginous foamable composition," etc. as used herein interchangeably refer to a composition that has the organoleptic character of an oily substance, i.e., oily feeling, when topically administered to a body area, such as the skin or mucosal tissue. Materials and properties for the oleaginous compositions and emulsions are described. Although the description that follows may refer to an oleaginous composition, it is understood that the materials are also suitable for use in an oleaginous emulsion, unless otherwise stated.

**[0038]** Surprisingly, the oleaginous compositions of the present invention require low surface active agent concentrations, e.g., less than 10% by weight and often much less, thus minimizing both undesirable irritation and costly raw material usage. The foamable compositions are light weight, have low density, spread easily and comfortably over large body area, and are thus, very convenient to use and economical.

**[0039]** The oleaginous compositions of the present invention include at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof, which provides a refatting and skin soothing effect. In one or more embodiments, the composition comprises at least 30% of said at least one solvent. In one or more embodiments, the composition comprises at least 50% of said at least one solvent. In one or more embodiments, the composition comprises at least 65% of said at least one solvent. The selected solvents allow the inclusion of oil-soluble active agents in the formulation. In one or more embodiments, the solvents provide synergistic benefits in combination with the active agent. The compositions may comprise at least one oil soluble active agent.

**[0040]** In one or more embodiments, the compositions require only low concentrations of a foaming agent in order to generate a stable foam. The reduced surface active agent requirement is advantageous since surface active agents are known to be irritating when in contact with the skin at elevated concentrations.

**[0041]** The foamable compositions are easily spreadable, allowing treatment of large areas such as the arms, back, trunk, legs and the breast. Furthermore, due to enhanced flow properties, they spread effectively into folds and wrinkles and absorb into the skin, providing uniform distribution of the active agent without the need of extensive rubbing thus providing an attractive means for the treatment of large body areas. The foamable compositions may be further used for the treatment of body cavities, such as the vagina,



penile urethra, rectum and the ear channel due to their expansion properties. In one or more embodiments the foamable compositions may be further used for transdermal delivery of drugs.

#### Class A foam composition

**[0042]** According to one aspect the present invention provides an oleaginous foam composition for topical application including:

at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof, at a concentration of about 70% to about 96.5% by weight,

at least a non-ionic surface active agent at a concentration of about 0.1% to about 10% by weight and, optionally, having an HLB value of about 9 or less;

optionally, at least one gelling agent at a concentration of about 0.1% to about 5% by weight;

at least one active agent at a therapeutically effective concentration; and

a propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0043]** The balance of the composition contains water and additional optional components. The content of the foam composition is presented herein as concentration (percent by weight, % w/w). The foam composition can be a homogeneous mixture or an emulsion.

**[0044]** Such a composition is placed in a pressurized aerosol container and, upon release from the container, creates a novel therapeutically-beneficial foam product.

**[0045]** Low water content provides high skin and body tissue lubrication, refatting, regulating residence of an active ingredient in the skin effects and effective skin absorption of a active agents. It is also helps to avoid degradation of water sensitive active agents.

**[0046]** Thus, in one or more embodiments, the oleaginous composition includes water at a concentration of about 30% or less, or at a concentration less than about 20%, or at a concentration less than about 10% by weight.

**[0047]** The oleaginous composition is optionally substantially free of short chain alcohols, i.e. comprises less than about 5% by weight of a short chain alcohol having 5 or less carbon atom in its skeleton, and may further comprise a foam adjuvant.

**[0048]** According to one embodiment, the oleaginous composition contains a solvent selected from the group consisting of a hydrophobic solvent and an emollient and at

least one co-solvent. According to one embodiment, the co-solvent is an organic solvent other than a short chain alcohol, that dissolves in water. Non-limiting examples of such co-solvents include polyols, propylene glycol, glycerol, and other polyhydroxy solvents (polyols). Preferably, the composition includes glycerol as co-solvent. In one embodiment, the composition includes a hydrophobic solvent component and a co-solvent at a weight ratio in the range of about 4:1 and about 1:4, or about 2:1 to 1:2. In a further embodiment of the present invention, the co-solvent constitutes a continuous phase of the emulsion and a minor portion of water is included in the co-solvent phase.

**[0049]** Such a composition is placed in an aerosol container and, upon release from the aerosol container, creates a therapeutically-beneficial foam product.

Class B foam composition:

**[0050]** According to another aspect the present invention provides an oleaginous foam composition may be a water-in-oil emulsion, i.e., an emulsion having one phase including at least one hydrophobic component (oil phase) and one phase which includes water. Due to the fact that the continuous phase of the emulsion is the oil phase, the composition provides an oily feeling, regulating residence of an active ingredient in the skin properties and protective effects. Notably, while it is known that a composition with a continuous oil phase is unlikely to form foam without high amounts of surface active agents, the oleaginous water-in-oil emulsion surprisingly forms a stable foam with low density. In one or more embodiments, there is an overlap between the compositions of Class A and Class B, the distinction being that Class B compositions are formed as water-in-oil emulsions.

**[0051]** According to one embodiment, the water-in-oil emulsion composition contains:

at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof, at a concentration of about 30% to about 96% by weight,

water at a concentration of 1% to about 70% by weight;

at least one non-ionic lipophilic surface active agent, for example, having an HLB value of about 3 to about 10, more preferably about 3.5 to about 9 at a concentration of about 0.1% to about 10% by weight, or between about 0.1% and about 5% by weight, or even between about 0.1% and about 2% by weight;

optionally, at least one gelling agent at a concentration of about 0.1% to about 5% by weight;

at least one active agent at a therapeutically effective concentration; and

a propellant at a concentration of about 3% to about 25% by weight of the total composition, in an aerosol container.

**[0052]** According to a further embodiment, the ratio between the oil phase and water is between about 1:3 and about 6:1.

**[0053]** An oleaginous foam emulsion is a composition having at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof in the continuous phase of the composition and is characterized by an oily feeling upon application to a body surface.

**[0054]** An oleaginous composition or emulsion may provide an enhanced regulating residence of an active ingredient in the skin effect, which may in turn control the drug residence time and skin penetration of an active agent. Furthermore, oleaginous compositions and emulsions provide moisturizing effects, refatting effects, protective effects and lubrication, all of which contribute to the treatment of dermatological disorders. Thus, a composition of this nature, comprising an oleaginous vehicle and an active agent is expected to provide a synergistic therapeutic effect.

#### Solvents

**[0055]** The solvent of the composition of the present invention is selected from the group consisting of a hydrophobic solvent, an emollient, a silicone oil, a co-solvent, and a mixture thereof. The solvent occupies at least the continuous phase; however, it may also partition into the discontinuous phase in those instances when the composition is an emulsion.

#### Hydrophobic solvent

**[0056]** A "hydrophobic solvent" as used herein includes but is not limited to a material having solubility in distilled water at ambient temperature of less than about 1 gm per 100 mL, or less than about 0.5 gm per 100 mL, or even less than about 0.1 gm per 100 mL. It is liquid at ambient temperature. The identification of a hydrophobic solvent by its solubility in water is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of

materials suitable for use as a hydrophobic solvent in the foamable compositions described herein.

**[0057]** In one embodiment, the solvent is a hydrophobic solvent such as mineral oil. Mineral oil (Chemical Abstracts Service Registry number 8012-95-1) is a mixture of aliphatic, naphthalenic, and aromatic liquid hydrocarbons that derive from petroleum. They are typically liquid; their viscosity is in the range of between about 35 CST and about 100 CST (at 40°C); and their pour point (the lowest temperature at which an oil can be handled without excessive amounts of wax crystals forming so preventing flow) is below 0°C. By contrast, white petrolatum, also termed "Vaseline", is disadvantageous, due to the waxy nature and semi-solid texture of petrolatum. It is known to leave a waxy and sticky feeling after application and occasionally stain cloths. Thus, white petrolatum as well as other wax-like, semi-solid compounds are undesirable as a hydrophobic solvent according to the present invention.

**[0058]** According to one embodiment, the oleaginous foam composition of the present invention includes a hydrophobic solvent selected from mineral oil, a triglyceride oil, an ester of a fatty acid, an ester of a dicarboxylic acid, silicone oil, a polyunsaturated oil, an unsaturated oil and an essential oil.

**[0059]** According to one embodiment, hydrophobic solvents are liquid oils originating from vegetable, marine or animal sources. The hydrophobic solvent may be selected from the group consisting of a saturated or an unsaturated oil. Preferably, the unsaturated oil is selected from the group consisting of an olive oil, a corn oil, a soybean oil, a canola oil, a cottonseed oil, a coconut oil, a sesame oil, a sunflower oil, a borage seed oil, an *syzigium aromaticum* oil, a hempseed oil, a herring oil, a cod-liver oil, a salmon oil, a flaxseed oil, a wheat germ oil, an evening primrose oil and any mixtures thereof, at any proportion.

**[0060]** One class of hydrophobic solvents includes, but is not limited to, polyunsaturated oils, containing omega-3 and omega-6 fatty acids, which are known to possess therapeutic properties through different modes of action. Examples of such polyunsaturated fatty acids are linoleic and linolenic acid, gamma-linoleic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Thus, in one embodiment of the present invention the hydrophobic solvent includes at least 6% of an oil selected from omega-3 oil, omega-6 oil, and mixtures thereof.

**[0061]** Another class of hydrophobic solvents is the essential oils, which are considered "therapeutic oils." Therapeutic oils contain active biologically occurring

molecules and, upon topical application, exert a therapeutic effect. Examples of such oils are rosehip oil, which contain retinoids and is known to reduce acne and post-acne scars, and tea tree oil, which possesses anti-microbial activity including antibacterial, antifungal and antiviral properties. Other examples of essential oils are basil, camphor, cardamom, carrot, citronella, clary sage, clove, cypress, frankincense, ginger, grapefruit, hyssop, jasmine, lavender, lemon, mandarin, marjoram, myrrh, neroli, nutmeg, petitgrain, sage, tangerine, vanilla, verbena, as well as any other therapeutically beneficial oil known in the art of herbal medication.

#### Emollient

**[0062]** A further class of solvents is "emollients" that have a softening, refatting, or soothing effect, especially when applied to body areas, such as the skin and mucosal surfaces. Emollients are not necessarily hydrophobic, nor are they necessarily solubilizing of the active agent or other components of the foamable compositions described herein. Without derogating the generality of this definition, examples of suitable emollients for use include hexyleneglycol, propylene glycol, isostearic acid derivatives, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, sucrose esters of fatty acids, octyl hydroxystearate and mixtures thereof. Examples of other suitable emollients may be found in the Cosmetic Bench Reference, pp. 1.19-1.22 (1996).

#### Silicone oil

**[0063]** Silicone oils possess skin protective properties and readily facilitate regulating residence of an active ingredient in the skin regulating residence of an active ingredient in the skin. Silicone oil may be either a volatile silicon oil or a non-volatile silicone oil. Water-soluble silicones, such as dimethicone copolyol are not included in the definition of silicone oils (as hydrophobic solvents) according to the present invention. In one embodiment, the hydrophobic solvent includes at least 2% (w/w) silicone oil, or at least 5% (w/w) silicone oil.

**[0064]** Any mixture, in any proportion of hydrophobic solvents as listed herein can be used.

Co-solvent

**[0065]** A "co-solvent", in the context of the present invention is an organic solvent, other than a short chain alcohols, typically soluble in both water and oil. Examples of co-solvents, according to the present invention include polyols, sulfoxides, oleates, lactam compounds, esters, amides, alkanolic acids, and alkanols and admixtures thereof. Exemplary polyols include glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpenols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, and other glycols. Exemplary sulfoxides include dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, and dimethylacetamide. Exemplary oleates include monooleates of ethoxylated glycerides (with 8 to 10 ethylene oxide units) and triolein. Exemplary lactam compounds include azone (1-dodecylazacycloheptan-2-one) and 2-(n-nonyl)-1,3-dioxolane. Exemplary esters include isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl propionate, capric/caprylic triglycerides, octylmyristate, and dodecylmyristate. Exemplary amides include acetamide. Other suitable co-solvents include myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; various alkanolic acids such as caprylic acid and alkanols, such as dialkylamino acetates.

**[0066]** According to one embodiment, the co-solvent is a polyethylene glycol (PEG) or a PEG derivative, and mixtures thereof, that are flowable at ambient temperature, including PEG200 (MW about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof, provided, however, that said PEG or mixture of PEGs is flowable at ambient temperature. By "flowable", as that term implies, the polyethylene glycol may be viscous at ambient temperature. The PEG or PEG mixture can have a viscosity of about 20,000cps at ambient, or less than about 10,000 cps at ambient.

**[0067]** In one or more embodiments, the solvent is a mixture (e.g., an emulsion) of a hydrophobic solvent and glycerin, as described, for example, in US Pat. No.6,544,530 to Friedman. The ratio of hydrophobic solvent to glycerin can range from about 1:4 to about 4:1, and more preferably from about 1:2 to about 2:1.

**[0068]** In several cases, a given solvent can be defined as both emollient and co-solvent. A co-solvent may also be a potent solvent for selected active agents.

### Potent solvent

**[0069]** In one or more embodiments of the present invention, the foamable composition includes a potent solvent, in addition to or in place of one of the hydrophobic solvents, co-solvents and emollients of the composition. A potent solvent is a solvent other than mineral oil that solubilizes a specific active agent substantially better than a hydrocarbon solvent such as mineral oil or petrolatum. For example, a potent solvent solubilizes the active agent 5 fold better than a hydrocarbon solvent; or even solubilizes the active agent 10-fold better than a hydrocarbon solvent. The solubility of a given active agent in the potent solvent relative to its respective solubility in mineral oil is determined in the absence of the composition. That is, the potent solvent alone solubilizes the active agent better than the the mineral oil alone. This is an independent test, irrespective of the composition in which the potent solvent is incorporated.

**[0070]** In one or more embodiments of the present invention, the composition includes at least one active agent in a therapeutically effective concentration and at least one potent solvent in a sufficient amount to substantially solubilize the at least one active agent in the composition. The term "substantially soluble" means that at least 95% of the active agent has been solubilized, i.e., 5% or less of the active agent is present in a solid state. In one or more embodiments, the concentration of the at least one potent solvent is more than about 40% of the at least one solvent of the composition of the present invention; or even more than about 60%.

**[0071]** Non-limiting examples of pairs of active agent and potent solvent include:

Betamethasone valerate/ glycofurol: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol.

Hydrocortisone butyrate/ glycofurol: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol.

Metronidazole/dimethyl isosorbide: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in dimethyl isosorbide.

Ketoconazole/dimethyl isosorbide: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, propylene glycol and dimethyl isosorbide.

Mupirocin/various solvents: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, hexylene glycol, dimethyl isosorbide, propylene glycol and polyethylene glycol 400 (PEG 400).

Meloxicam, a nonsteroidal anti-inflammatory agent/propylene glycol: Practically insoluble in mineral oil (<0.001%); soluble in propylene glycol: 0.3 mg/mL; and in PEG

400: 3.7 mg/mL.

Progesterone/PEG 400: Practically insoluble in mineral oil (<0.001%); soluble in PEG 400: 15.3 mg/mL.

**[0072]** A non-limiting exemplary list of solvents that can be considered as potent solvents includes polyols, polyethylene glycol (PEG), propylene glycol, hexylene glycol, butanediols and isomers thereof, glycerol, benzyl alcohol, DMSO, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, such as dimethyl isosorbide, glycofurool and ethoxydiglycol (transcutol) and mixtures thereof in any proportion.

**[0073]** In another aspect, the present invention provides a method of designing a stable oleaginous foamable composition by selecting at least one active agent and identifying a solvent that solubilizes the active agent substantially better than mineral oil or petrolatum, for example, solubilizes the active agent 5-fold better or even 10-fold better than a hydrocarbon solvent such as mineral oil or petrolatum. The method may further include adjusting the type and concentration of surface active agent and gelling agent to provide a foamable composition.

**[0074]** The use of a potent solvent in a foam composition provides an improved method of delivering poorly soluble therapeutic agents to a target area. It is known that low drug solubility results in poor bioavailability, leading to decreased effectiveness of treatment. Foam compositions of the present invention, for which the solvent includes a potent solvent, increase the levels of the active agent in solution and thus, provide high delivery and improved therapy.

**[0075]** Potent solvents, as defined herein, are usually liquid. Formulations comprising potent solvents and active agents are generally disadvantageous as therapeutics, since their usage involves unwanted dripping and inconvenient method of application, resulting in inadequate dosing. The foams described herein are drip-free, provide a superior vehicle for such active agents, and enable convenient usage and accurate effective dosing.

**[0076]** The solvent of the present invention may include a mixture of the above solvents selected from the group of hydrophobic solvents, silicone oils, emollients co-solvents and potent solvents in any proportion.

Surface-active agents



**[0077]** Surface-active agents may include an agent useful in forming an emulsion and/or evolving a foam. A surface active agent's hydrophilic/lipophilic balance (HLB) describes the surface active agent's affinity towards water or oil. The HLB scale ranges from about 1 (totally lipophilic) to 45 (totally hydrophilic) and in the case of non-ionic surface active agents from 1 to 20 (totally hydrophobic), with 10 representing an equal balance of both hydrophilic and lipophilic characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions, hydrophilic surface active agents 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 (e.g., a weighted average).

**[0078]** Without wishing to be bound by any particular theory or mode of operation, hydrophilic surface active agents produce oil-in-water (o/w) microemulsions, whereas lipophilic surface active agents are used to promote emulsification of the aqueous phase into the oil phase.

**[0079]** The oleaginous composition of the present invention according to one or more embodiments includes at least one surface active agent or surface active agent, which is intended to both stabilize the formulation and to evolve an acceptable foam.

**[0080]** A composition having a low concentration of an ionic surface active agent is desirable in terms of safety, since high concentrations of surface active agents are known to evolve skin and mucosal membrane irritation. Unlike certain foamable oleaginous compositions of the art, the total surface active agent employed to obtain foam that is stable, of low specific gravity and has a fine bubble structure is relatively low. Low surface active agent levels, particularly of ionic surface active agents, are helpful in minimizing skin irritations. Total surface active agent may be in the range of about 0.1% to less than about 10% of the foamable composition, and is typically less than about 5%, or even less than about 2%. Yet, in one or more embodiments, when the composition comprises a liquid polar polyol or polyol mixture, such as polyethylene glycol, a foam can be produced even without a surface active agent.

**[0081]** According to one or more embodiments, the surface active agent is selected from hydrophilic, hydrophobic, and a mixture of hydrophilic and hydrophobic surface active agents. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. A combination of surface-active agents is possible.

**[0082]** According to one or more embodiments, suitable surface active agents for formation of a water-in-oil emulsion have an HLB value of no greater than 10, and for

example from about 3 to about 9. Thus, the composition may include a single surface-active agent having an HLB value between 3 and 9, or a mixture of surface-active agents having a weighted average of their HLB values between 3 and 9.

**[0083]** Suitable water-in-oil surface active agents include, but are not limited to, sorbitan derivatives such as sorbitan laurate and sorbitan palmitate; alkoxyated alcohols such as laureth-4; hydroxylated derivatives of polymeric silicones, such as dimethicone copolyol; alkylated derivatives of hydroxylated polymeric silicones, such as cetyl dimethicone copolyol; glyceryl esters such as polyglyceryl-4 isostearate; beeswax derivatives such as sodium isostearoyl-2-lactylate; lecithin; and mixtures thereof. In conjunction with the oil component being a silicone oil, the preferred emulsifiers are hydroxylated derivatives of polymeric silicones and alkylated derivatives thereof.

**[0084]** According to one or more embodiments the present invention, the composition comprises at least one non-ionic surface active agent. In one or more embodiments, the composition includes at least one non-ionic surface active agent and at least one ionic surface active agent selected from the group consisting of an anionic surface active agent, a cationic surface active agent and a zwitterionic surface active agent, at a weight ratio of between about 1:1 and about 20:0.1, or preferably at a weight ratio of about 4:0.1 to about 20:0.1.

**[0085]** The choice of specific surface active agents should be made keeping in mind the particular hydrophobic therapeutic agent to be used in the composition, and the range of polarity appropriate for the chosen therapeutic agent. With these general principles in mind, a very broad range of surface active agents is suitable.

**[0086]** Additional non-limiting examples of possible surface active agents include polysorbates, such as polyoxyethylene (20) sorbitan monostearate (Tween 60) and polyoxyethylene (20) sorbitan monooleate (Tween 80); Polyoxyethylene (POE) fatty acid esters, such as Myrj 45, Myrj 49 and Myrj 59; poly(oxyethylene) alkyl ethers, 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 sorbitol anhydrides, such as sorbitan monolaurate and sorbitan monolaurate; fatty alcohols or acids, mono or diglycerides, isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines, provided that, in the case of a single surface active agent, the HLB value is between 3 and 9; and in the case of a mixture of surface-active agents, the weighted average of their HLB values is between 3 and 9.

**[0087]** In one or more embodiments, the at least one surface active agent is a phospholipid. In a one or more embodiments, the phospholipid is phosphatidylcholine or 1,2-diacyl-sn-glycerol-3-phosphorylcholine, also termed "lecithin", which is a naturally occurring phospholipid which possesses surface active agent properties. Lecithin is the most abundant lipid in the membranes of biological tissues and as such, is considered a non-irritant. Lethicin is a phospholipid composition very similar in composition to that of human skin. For this reason, it is possible to use lethicin as an emulsifier or a surfact-active agent at levels about 10% by weight. In one or more embodiments, the surface-active agent includes lethicin up to about 10% by weight and the total surfact-active agent (when a mixture of agents is used) can be up to 15% by weight.

**[0088]** A composition having a low concentration of an ionic surface active agent, or even no ionic surface active agent, is desirable in terms of safety, since high concentrations of surface active agents are known to evolve skin irritation.

#### Gelling agents

**[0089]** The composition according to one or more embodiments of the present invention include at least one gelling agent at a concentration of about 0.1% to about 5%. The at least one gelling agent is selected from the group consisting of a natural polymeric material, a semi-synthetic polymeric material, a synthetic polymeric material, an inorganic gelling agent and mixtures thereof. Yet, in one or more embodiments, a foam with favorable properties can be produced even without a gelling agent.

**[0090]** Exemplary gelling agents that can be used in accordance with one or more embodiments of the present invention include for example, but are not limited to, 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, starch, chemically modified starches and the like, semi-synthetic polymeric materials such as cellulose ethers (e.g. hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, hydroxy propylmethyl cellulose), polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guar and the like and synthetic polymeric materials such as carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like. Optionally, mixtures of the above compounds are contemplated.

**[0091]** It has been surprisingly discovered that certain gelling agents provide foam compositions that produce foams with high foam stability and an appealing organoleptic feel, even in the absence of foam stabilizing agents such as fatty acids and fatty alcohols. The gelling agent is selected from the class of amphiphilic copolymers. Amphiphilic copolymers include polymers having hydrophobic groups and hydrophilic groups or regions. These materials are referred to alternatively as "polymeric surfactants" because the hydrophilic and hydrophobic regions of the polymers serve to interact with and stabilize hydrophilic and lipophilic components, respectively, of a composition. The copolymer may be a random copolymer, a block copolymer of a graft or comb copolymer. Exemplary amphiphilic copolymers include di-, tri- or multi-block copolymer or graft copolymer of a biodegradable polymer.

**[0092]** The polymeric surfactant may be an acrylate copolymer, in which hydrophobic moieties are chemically linked to hydrophilic polymer or hydrophilic moieties are attached to hydrophobic polymers to produce amphiphilic surface active and surface stabilizing agent. By way of example, suitable polymeric surfactants include cross linked copolymers of acrylic acid and a hydrophobic comonomer, such as Pemulen TR-1 and Pemulen TR-2, ETD 2020 and Carbopol 1382 (all, Acrylates/C10-30 alkyl acrylate crosspolymer), Natrosol CS Plus 330 and 430 and Polysurf 67 ( all, cetyl hydroxyethyl cellulose), Aculyn 22 (acrylates /steareth-20 methacrylate copolymer), Aculyn 25 (acrylates/ laureth-25 methacrylate copolymer), Aculyn 28 (acrylates /behent-25 methacrylate copolymer), Aculyn 46 (PEG-150/stearyl alcohol/SMDI copolymer), Stabylen 30 (acrylates/vinyl isodecanoate), Structure 2001 (acrylates/steareth-20 itaconate copolymer), Structure 3001 (acrylates/ceteth-20 itaconate copolymer) and Structure Plus (acrylates/aminoacrylates/C10-30 alkyl PEG 20 itaconate copolymer), where PEG is polyethylene glycol, PPG is polypropylene glycol.

**[0093]** Other exemplary amphiphilic copolymers include silicone polymers such as amphiphilic silicone polyols or copolyol, for example cetyl dimethicon copolyol and dimethicone copolyol PPG-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starches, and amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol (also known as "poloxamer").

**[0094]** The gelling agent may include other types of gelling agents, in combination with an amphiphilic copolymer. For example, naturally-occurring thickening agents may be included. Exemplary polymeric materials include locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum sodium alginate, xanthan

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

**[0095]** The amphiphilic copolymer may be selected from the group consisting of Pemulen polymeric surfactants, acrylates/C10-30 alkyl acrylate crosspolymer, cetyl hydroxyethyl cellulose, acrylates /steareth-20 methacrylate copolymer, acrylates/ laureth-25 methacrylate copolymer, acrylates /beheneth-25 methacrylate copolymer, PRG-150/stearyl alcohol/SMDI copolymer, acrylates/vinyl isodecanoate, acrylates/steareth-20 itaconate copolymer, acrylates/ceteth-20 itaconate copolymer and acrylates/aminoacrylates/C10-30 alkyl PEG 20 itaconate copolymer, amphiphilic silicone polymers, alkyl dimethicon copolyol, cetyl dimethicon copolyol, dimethicone copolyol PPG-3 oleyl ether, acetylated starch derivatives, amphiphilic modified starches, and amphiphilic block copolymers of ethylene oxide, propylene oxide and/or propylene glycol.

**[0096]** Further exemplary gelling agents include the acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers sold, for example, by the B.F. Goodrich Company under the trademark of Carbopol® resins. These resins consist essentially of a colloidal water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with from 0.75% to 2% of a crosslinking agent such as polyallyl sucrose or polyallyl pentaerythritol. Examples include Carbopol® 934, Carbopol® 940, Carbopol® 950, Carbopol® 980, Carbopol® 951 and Carbopol® 981. Carbopol® 934 is a water-soluble polymer of acrylic acid crosslinked with about 1% of a polyallyl ether of sucrose having an average of about 5.8 allyl groups for each sucrose molecule.

**[0097]** Yet, another group of gelling agents includes, but is not limited to, inorganic gelling agents, such as silicone dioxide (fumed silica) including but not limited to AEROSIL 200 (DEGUSSA).

**[0098]** The gelling agent is present in an amount in the range of about 0.1% to about 5.0 wt% of the foamable composition. In one or more embodiments, it is typically less than 1 wt% of the foamable composition.

**[0099]** The gelling agent is present in the foam carrier or composition in an amount of about 0.1 to 5.0 wt% by weight. The gelling agent included in the foamable composition can be less than 1 wt% by weight of the foamable oleaginous composition.

#### Foam adjuvants

**[00100]** The oleaginous composition of the present invention may optionally further include at least one foam adjuvant. In one or more embodiments, foam adjuvants include 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 oleyl alcohol (C18, unsaturated), arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). The concentration of the fatty alcohol that is required to support the foam system is inversely related to the length of its carbon chains. Fatty alcohols derived from beeswax 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 adjuvants according to the present invention.

**[00101]** Another class of foam adjuvants, according to one or more embodiments of the present invention, 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.

**[00102]** 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 according to the present invention comprises a long chain fatty alcohol or fatty acid, wherein the carbon atom chain is branched. In an additional preferred class of foam adjuvants, the carbon chain of said fatty acid is substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

**[00103]** The foam adjuvant according to the present invention may comprise a mixture of fatty alcohols, fatty acids and hydroxy fatty acids and derivatives thereof in any proportion, providing that the total concentration is about 0.1% to about 10% (w/w) preferably about 0.1% to about 5% (w/w) in one or more embodiments, the total concentration is about 0.4% to about 2.5% (w/w) of the total composition.

**[00104]** A feature of fatty alcohols and fatty acids relevant to their use in the foamable compositions according to one or more embodiments of the present invention is related to their therapeutic properties per se. Long chain saturated and mono unsaturated fatty alcohols, e.g., stearyl alcohol, ercyl alcohol, arachidyl alcohol and docosanol have been reported to possess antiviral, anti infective, anti-proliferative and anti-inflammatory

properties (US Patent No. 4,874,794). Longer chain fatty alcohols, e.g., tetracosanol, hexacosanol, heptacosanol, octacosanol, triacontanol, etc. are also known for their metabolism modifying properties and tissue energizing properties. Long chain fatty acids have also been reported to possess anti-infective characteristics. Thus, the pharmaceutical or cosmetic composition of the present invention including the optional foam adjuvant provides an extra or added therapeutic benefit.

#### Water content

**[00105]** The creation of a foamable composition with low water content is not easy, and usually requires very high concentrations of a foaming surface active agent system, which may comprise a high proportion of ionic surface active agents. However, ionic surface active agents are known to be skin irritants in a concentration-dependent manner, and thus, their use in the treatment of sensitive skin and other body tissues is very limited. Surprisingly, the oleaginous compositions of the present invention have a low water content, and yet require very low concentration of surface active agents, which are primarily non-ionic.

#### Substantially alcohol free

**[00106]** Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton, such as ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol and pentanol are considered less desirable solvents or co-solvents due to their skin-irritating effect. Thus, the composition of the present invention is substantially alcohol-free have less than about 5% final concentration of short chain alcohols, or less than 2%, or even less than 1%.

#### Optional Ingredients

**[00107]** The pharmaceutical or cosmetic composition of the present invention optionally includes a variety of therapeutic or cosmetic ingredients, which are added in order to fine-tune the consistency of the formulation, protect the formulation components from degradation and oxidation and bestow their cosmetic acceptability. Such an excipient is preferably selected from the group consisting of a diglyceride, a triglyceride, a stabilizing agent, an antioxidant, glycerol, a flavoring, a colorant agent an odorant agent and any other formulation component known in the art of pharmaceutical and cosmetic formulary. The pharmaceutical or cosmetic composition is very easy to use. When applied onto the afflicted body surface of humans or animals, it is in a foam state, allowing free application without drip or 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.

#### Active agents

**[00108]** It is to be understood that the active agents useful herein can in some instances provide more than one benefit or operate via more than one mode of action. Therefore, classifications herein are made for the sake of convenience and are not intended to limit the active agent to that particular application or applications listed.

**[00109]** The foam composition is useful and advantageous for the treatment of skin disorders and for skin care and cosmetic care. The addition of an oil having refatting, protective and moisture-retaining properties in a spreadable foam form can substitute for currently available dermatological and cosmetic creams, lotions, gels, etc.

**[00110]** In one or more embodiments of the present invention, the foam includes an active agent directed to the treatment of a medical disorder or a cosmetic disorder. The active agent can be categorized by the benefit it provides or by its postulated mode of action. The active agents can in some instances provide more than one benefit or operate via more than one mode of action. Therefore, classifications are made for the sake of convenience and are not intended to limit the active to that particular application or applications listed. Furthermore, foam compositions, with or without further active ingredients, are suitable for the application as "cosmeceutical" preparations.

**[00111]** The composition of the present invention includes at least one active agent that provides therapeutic or cosmetic activity.

**[00112]** The composition of the present invention having at least one "active agent", provides the following benefits:

favorable spreadability and absorption, compared to conventional ointment, cream, lotion and the like; improved treatment convenience, leading to better compliance;

enhanced delivery, leading to elevated bioavailability of the drug or cosmetic active agent in the target organ, thereby improving treatment efficacy.

**[00113]** In the context of the present invention, pharmaceutical and cosmetic active agents are included under the definition of at least one active agent. According to one embodiment the at least one active agent may be a single agent or a combination of agents that can be dissolved in the oleaginous carrier composition.

**[00114]** According to one embodiment, the at least one active agent is a hydrophobic agent, having solubility in distilled water at ambient temperature of less than about 1 gm



per 100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL. In another embodiment, the at least one active agent is any therapeutic or cosmetic agent, providing that it is encapsulated in a hydrophobic envelope.

**[00115]** In another embodiment, the at least one active agent is insoluble and thus, incorporated in the foamable carrier of the present invention by suspension.

**[00116]** Non-limiting examples of active agents include antibiotic, antibacterial, antifungal, antiviral, antiinflammatory, anesthetic, analgesic, antiallergic, corticosteroid, retinoidretinoids, lubricating agents and antiproliferative medications and mixtures thereof at any proportion. The concentration of said agents may be adopted to exert a therapeutic effect on a disease when applied to an afflicted area.

**[00117]** A general non-limiting list of hydrophobic active agents include abacavir, acebutolol, acrivastine, alatrofloxacin, albuterol, albendazole, alprazolam, alprenolol, amantadine, amiloride, aminoglutethimide, amiodarone, amitriptyline, amlodipine, amodiaquine, amoxapine, amphetamine, amphotericin, amprenavir, amrinone, amsacrine, astemizole, atenolol, atropine, azathioprine, azelastine, azithromycin, baclofen, benethamine, benidipine, benzhexol, benznidazole, benztropine, biperiden, bisacodyl, bisanthrene, bromazepam, bromocriptine, bromperidol, brompheniramine, brotizolam, bupropion, butenafine, butoconazole, cambendazole, camptothecin, carbinoxamine, cephadrine, cephalixin, cetirizine, cinnarizine, chlorambucil, chlorpheniramine, chlorproguanil, chlordiazepoxide, chlorpromazine, chlorprothixene, chloroquine, cimetidine, ciprofloxacin, cisapride, citalopram, clarithromycin, clemastine, clemizole, clenbuterol, clofazimine, clomiphene, clonazepam, clopidogrel, clozapine, clotiazepam, clotrimazole, codeine, cyclizine, cyproheptadine, dacarbazine, darodipine, decoquinatate, delavirdine, demeclocycline, dexamphetamine, dexchlorpheniramine, dexfenfluramine, diamorphine, diazepam, diethylpropion, dihydrocodeine, dihydroergotamine, diltiazem, dimenhydrinate, diphenhydramine, diphenoxylate, diphenylimidazole, diphenylpyraline, dipyridamole, dirithromycin, disopyramide, dolasetron, domperidone, donepezil, doxazosin, doxycycline, droperidol, econazole, efavirenz, ellipticine, enalapril, enoxacin, enrofloxacin, eperisone, ephedrine, ergotamine, erythromycin, ethambutol, ethionamide, ethopropazine, etoperidone, famotidine, felodipine, fenbendazole, fenfluramine, fenoldopam, fentanyl, fexofenadine, flecainide, flucytosine, flunarizine, flunitrazepam, fluopromazine, fluoxetine, flupenthixol, flupenthixol decanoate, fluphenazine, fluphenazine decanoate, flurazepam,

flurithromycin, frovatriptan, gabapentin, granisetron, grepafloxacin, guanabenz, halofantrine, haloperidol, hyoscyamine, imipenem, indinavir, irinotecan, isoxazole, isradipine, itraconazole, ketoconazole, ketotifen, labetalol, lamivudine, lansoprazole, leflunomide, levofloxacin, lisinopril, lomefloxacin, loperamide, loratadine, lorazepam, lormetazepam, lysuride, mepacrine, maprotiline, mazindol, mebendazole, meclizine, medazepam, mefloquine, melonicam, meptazinol, mercaptopurine, mesalamine, mesoridazine, metformin, methadone, methaqualone, methylphenidate, methylphenobarbital, methysergide, metoclopramide, metoprolol, metronidazole, mianserin, miconazole, midazolam, miglitol, minoxidil, mitomycins, mitoxantrone, molindone, montelukast, morphine, moxifloxacin, nadolol, nalbuphine, naratriptan, natamycin, nefazodone, nelfinavir, nevirapine, nicardipine, nicotine, nifedipine, nimodipine, nimorazole, nisoldipine, nitrazepam, nitrofurazone, nizatidine, norfloxacin, nortriptyline, nystatin, ofloxacin, olanzapine, omeprazole, ondansetron, amidazole, oxamniquine, oxantel, oxatomide, oxazepam, oxfendazole, oxiconazole, oxprenolol, oxybutynin, oxyphencyclimine, paroxetine, pentazocine, pentoxifylline, perchlorperazine, perfloxacin, perphenazine, phenbenzamine, pheniramine, phenoxybenzamine, phentermine, physostigmine, pimozone, pindolol, pizotifen, pramipexol, pranlukast, praziquantel, prazosin, procarbazine, prochlorperazine, proguanil, propranolol, pseudoephedrine, pyrantel, pyrimethamine, quetiapine, quinidine, quinine, raloxifene, ranitidine, remifentanyl, repaglinide, reserpine, ricobendazole, rifabutin, rifampin, rifapentine, rimantadine, risperidone, ritonavir, rizatriptan, ropinirole, rosiglitazone, roxaditine, roxithromycin, salbutamol, saquinavir, selegiline, sertraline, sibutramine, sildenafil, sparfloxacin, spiramycins, stavudine, sulconazole, sulphasalazine, sulphiride, sumatriptan, tacrine, tamoxifen, tamsulosin, temazepam, terazosin, terbinafine, terbutaline, terconazole, terfenadine, tetramisole, thiabendazole, thioguanine, thioridazine, tiagabine, ticlopidine, timolol, tinidazole, tioconazole, tirofiban, tizanidine, tolterodine, topotecan, toremifene, tramadol, trazodone, triamterene, triazolam, trifluoperazine, trimethoprim, trimipramine, tromethamine, tropicamide, trovafloxacin, vancomycin, venlafaxine, vigabatrin, vinblastine, vincristine, vinorelbine, vitamin K5, vitamin K6, vitamin K7, zafirlukast, zolmitriptan, zolpidem, zopiclone, acetazolamide, acetohexamide, acrivastine, alatrofloxacin, albuterol, alclofenac, aloxiprin, alprostadil, amodiaquine, amphotericin, amylobarbitol, aspirin, atorvastatin, atovaquone, baclofen, barbitol, benazepril, bezafibrate, bromfenac, bumetanide, butobarbitol, candesartan, capsaicin, captopril, cefazolin, celecoxib, cephadrine, cephalixin, cerivastatin, cetirizine,

chlorambucil, chlorothiazide, chlorpropamide, chlorthalidone, cinoxacin, ciprofloxacin, clonofibrate, cloxacillin, cromoglicate, cromolyn, dantrolene, dichlorophen, diclofenac, dicloxacillin, dicumarol, diflunisal, dimenhydrinate, divalproex, docusate, dronabinol, enoximone, enalapril, enoxacin, enrofloxacin, epalrestat, eposartan, essential fatty acids, estramustine, ethacrynic acid, ethotoin, etodolac, etoposide, fenbufen, fenoprofen, fexofenadine, fluconazole, flurbiprofen, fluvastatin, fosinopril, fosphenytoin, fumagillin, furosemide, gabapentin, gemfibrozil, gliclazide, glipizide, glybenclamide, glyburide, glimepiride, grepafloxacin, ibufenac, ibuprofen, imipenem, indomethacin, irbesartan, isotretinoin, ketoprofen, ketorolac, lamotrigine, levofloxacin, levothyroxine, lisinopril, lomefloxacin, losartan, lovastatin, meclofenamic acid, mefenamic acid, mesalamine, methotrexate, metolazone, montelukast, nalidixic acid, naproxen, natamycin, nimesulide, nitrofurantoin, non-essential fatty acids, norfloxacin, nystatin, ofloxacin, oxacillin, oxaprozin, oxyphenbutazone, penicillins, pentobarbital, perfloxacin, phenobarbital, phenytoin, pioglitazone, piroxicam, pramipexol, pranlukast, pravastatin, probenecid, probucol, propofol, propylthiouracil, quinapril, rabeprazole, repaglinide, rifampin, rifapentine, sparfloxacin, sulfabenzamide, sulfacetamide, sulfadiazine, sulfadoxine, sulfamerazine, sulfamethoxazole, sulfafurazole, sulfapyridine, sulfasalazine, sulindac, sulphasalazine, sulthiame, telmisartan, teniposide, terbutaline, tetrahydrocannabinol, tirofiban, tolazamide, tolbutamide, tolcapone, tolmetin, tretinoin, troglitazone, trovafloxacin, undecenoic acid, ursodeoxycholic acid, valproic acid, valsartan, vancomycin, verteporfin, vigabatrin, vitamin K-S (II), zafirlukast, and pharmaceutically acceptable oil-soluble derivative and salts thereof.

#### Anti-infective Agents

**[00118]** Anti-infective agents include antibacterial, antifungal, antiviral, and anti-parasitic agents.

#### Antibacterial agents

**[00119]** The term "antibacterial" 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 and other microorganisms, and are used in the treatment of infectious diseases.

**[00120]** One class of active agents is antibacterial agents. It is well known that bacterial infections are involved in a variety of superficial and non-superficial disorders of the skin and mucosal membranes. The antibacterial agent can be active against gram

positive and gram-negative bacteria, protozoa, aerobic bacteria and anaerobes. The composition may include one or a combination of water soluble, oil soluble and suspended antibacterial agents.

**[00121]** Specific oil-soluble species of macrolide antibiotics, such as erythromycin; sulfonamide (in its base form), such as sulfanilamide, sulfadiazine and sulfacetamide; mupirocin; tetracyclines, such as tetracycline and doxycycline; specific oil-soluble species of synthetic and semi-synthetic penicillins and beta-lactams; cloramphenicol; specific oil-soluble species of imidazoles; dicarboxylic acids, such as azelaic acid; salicylates; peptide antibiotics; cyclic peptides, such as cyclosporine, tacrolimus, pimecrolimus and sirolimus (rapamycin); and non-specific antibacterial agents such as strong oxidants and free radical liberating compounds, bleaching agents, iodine compounds and benzoyl peroxide.

**[00122]** Antibacterial compositions according to one or more embodiments of the present invention may be used to treat infections of the skin. An example of a very common skin infection is impetigo, a bacterial disease caused by *Staphylococcus aureus* and beta-hemolytic streptococci, which mainly afflicts children and infants. Various antibacterial creams and ointments, such as mupirocin cream and mupirocin ointment, have been utilized to treat impetigo, however, treatment compliance is markedly impaired due to the fact that children resist the extensive rubbing involved in cream and ointment treatment. Foam, on the other hand, was found to be easily applied, without any difficulty. It has been surprisingly discovered that a composition of mupirocin and a vehicle containing PEG (as a potent solvent), a non-ionic surface active agent and a gelling agent, where the non-ionic surface-active agent at a concentration of 2% by weight and the total amounts of surface-active agent is in the range of 2.5% by weight, and propellant, afforded an excellent foam which was stable upon discharge from the aerosol can and was easy to apply onto an afflicted area.

**[00123]** The composition according to one or more embodiments of the present invention is particularly useful and beneficial in the prevention and treatment of secondary infections, accompanying skin-structure damage, such as in cuts, wounds, burns and ulcers. In all such cases, the present formulation is easy to use, being in foam state upon application and absorbing into the skin instantly upon gentle application.

**[00124]** While being useful in the prevention and treatment of infections, the antibacterial foam of the present invention is also applicable for decontaminating areas, afflicted with bacterial warfare organisms, such as anthrax and smallpox.

#### Anti-fungal agents

**[00125]** Fungal infections are another object of treatment using the composition of the present invention. Superficial fungal infection of the skin is one of the most common skin diseases seen in general practice. Dermatophytosis is probably the most common superficial fungal infection of the skin. It is caused by a group of fungi capable of metabolizing the keratin of human epidermis, nails or hair. There are three genera of dermatophytes causing dermatophytosis, i.e, microsporum, trichophyton and epidermophyton.

**[00126]** Candidiasis is an infection caused by the yeast like fungus candida albicans or occasionally other species of candida. Clinical syndromes of candidiasis include: (a) oral candidiasis (thrush); (b) candidiasis of the skin and genital mucous membrane; and (c) candida paronychia, which inflicts the nail and nail bed; and (d) genital and vaginal candida, which inflict genitalia and the vagina.

**[00127]** Optionally, the pharmaceutical composition includes an antifungal drug, which antifungal drug provides effective treatment against dermatophytes and candida. The antifungal drug can be selected from the group consisting of azoles, diazoles, triazoles, miconazole, fluconazole, ketoconazole, clotrimazole, itraconazole griseofulvin, ciclopirox, amorolfine, terbinafine, Amphotericin B, potassium iodide, flucytosine (5FC) and any combination thereof at a therapeutically effective concentration.

**[00128]** The composition according to one or more embodiments of the present invention is useful for example for the treatment and prevention of tinea corporis, tinea pedis, tinea rubrum, tinea unguium, tinea cruris, tinea barbae and tinea versicolor, as well as yeast infections, such as candidiasis, and candidal vaginitis.

#### Anti-viral agents

**[00129]** The composition according to one or more embodiments of the present invention is particularly beneficial in treating and preventing viral infections. Cold sores are caused by the herpes simplex Type 1 virus and are sometimes referred to as facial herpes. Mollusca are small viral growths that appear singly or in groups on the face, trunk, lower abdomen, pelvis, inner thighs, or penis. Shingles (herpes zoster), usually occurs only once in a lifetime, appears as a rash (clusters of blisters with a red base).

Shingles is caused by the same virus responsible for chickenpox. Warts are a common, benign skin tumor caused by viral infection.

**[00130]** Any known antiviral agent, in a therapeutically effective concentration, can be incorporated in the foam composition according to one or more embodiments of the present invention. The composition according to one or more embodiments of the present invention includes a hydrophobic solvent for facilitating an enhanced rate of penetration and better topical distribution of any of the above listed antiviral drugs.

Anti-inflammatory and anti-allergic agents

**[00131]** Yet, according to another embodiment of the present invention the active agent is an anti-inflammatory or anti-allergic agent. An anti-inflammatory agents or antiallergic agent is selected from the group consisting of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), anti-histamines, immunosuppressant agents, immunomodulators; and any combination thereof at a therapeutically effective concentration.

**[00132]** The following table provides a summary of currently available corticosteroid agent and their typical therapeutically effective concentration.

Potency	Compound	Current products
Very high	Clobetasol propionate	Cream or ointment 0.05%
	Halobetasol propionate	Cream or ointment 0.05%
High	Betamethasone dipropionate	Cream or ointment 0.05%
	Betamethasone valerate	Ointment 0.1%
	Fluocinolone acetonide	Cream 0.02%
	Halcinonide	Cream or ointment 0.1%
Medium	Betamethasone valerate	Cream 0.1%
	Fluocinolone acetonide	Cream or ointment 0.020%
	Hydrocortisone valerate	Cream or ointment 0.2%
	Triamcinolone acetonide	Cream, ointment, or lotion 0.1% or 0.020%
Low	Hydrocortisone	Cream, ointment, or lotion 1.0% or 2.5%

**[00133]** The concentrations of corticosteroid drugs, as presented in the above table are provided herein only as example, and any therapeutically effective concentration of such corticosteroids can be incorporated in the composition of the present invention.

**[00134]** Since corticosteroid drugs are typically hydrophobic, the composition according to one or more embodiments of the present invention that includes a hydrophobic solvent is suitable as a vehicle to facilitate better topical distribution, improved occlusion and an enhanced rate of penetration of any of the above listed drugs.

**[00135]** Corticosteroids are used for treating psoriasis and atopic dermatitis (AD), common chronic inflammatory skin diseases, characterized by periodic flare-ups of sharply defined red patches covered by scaly patches (in the case of psoriasis) and inflamed skin in the case of AD.

**[00136]** It is envisaged that the composition according to one or more embodiments of the present invention may provide a treatment for Psoriasis and AD.

**[00137]** Corticosteroid ointments, greasy preparations containing little or no water, are typically used for treating psoriasis. Their main disadvantage is in their sticky feeling subsisting, for extended periods subsequent to treatment being completed. Thereby creating a latent inconvenience and possible discomfort to the treatment recipient. By contrast, the oleaginous foam composition according to one or more embodiments of the present invention, while possessing a considerable concentration of an oil (hydrophobic solvent), spreads very easily throughout the afflicted area and absorbs into the skin without leaving any untoward sensation or look.

**[00138]** Other non-limiting examples of inflammatory disorders, which can be prevented or are treatable by the oleaginous compositions according to one or more embodiments of the present invention, wherein the drug is a steroid are atopic dermatitis, seborrhea, seborrheic dermatitis of the face and trunk, seborrheic blepharitis, contact dermatitis, stasis dermatitis (gravitational eczema; varicose eczema), exfoliative dermatitis (erythroderma), lichen simplex chronicus, pityriasis rosea and pemphigus.

**[00139]** Certain of the solvents that may be used in the preparation of the composition according to one or more embodiments of the present invention include polyunsaturated fatty acids, containing omega-3 and omega-6 fatty acids (e.g., linoleic and linolenic acid, gamma-linoleic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are themselves beneficial in the treatment of psoriasis and other skin inflammation conditions.

**[00140]** Nonsteroidal anti-inflammatory agents (NSAIDs) are useful against skin abnormalities and may be added to the oleaginous foam compositions according to one or more embodiments of the present invention. The variety of compounds encompassed

by NSAIDs is well-known to those skilled in the art. Specific non-steroidal anti-inflammatory agents useful in the composition invention include, but are not limited to:

Oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam;

Salicylates, such as salicylic acid, ethyl salicylate, methyl salicylate, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;

Acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac;

Fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;

Propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, piroprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, and tiaprofenic; and

Pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

**[00141]** Any further steroidal and nonsteroidal compounds having the capacity to prevent, alleviate the symptoms of, treat or cure inflammation processes are generally included as possible anti-inflammatory agents, according to one or more embodiments of the present invention.

**[00142]** Topical antihistaminic preparations currently available include 1% and 2% diphenhydramine, 5% doxepin, phrilamine maleate, chlorpheniramine and tripeleminamine, phenothiazines, promethazine hydrochloride and dimethindene maleate. These active agents, as well as additional antihistamines, can also be incorporated in the composition according to one or more embodiments of the present invention.

**[00143]** The therapeutic composition according to one or more embodiments of the present invention optionally includes an anti-inflammatory and/or an antiallergic agent, wherein said agent reduces the occurrence of pro-inflammatory cytokines or inhibits the effect of pro-inflammatory cytokines.

**[00144]** It is envisaged that mixtures of any anti-inflammatory agents can be used, as well as the dermatologically acceptable salts, esters, amides, prodrugs and derivatives of these agents.

**[00145]** Topical application of an oleaginous foam including a safe and effective dose of an NSAID can be useful in the prevention and/or alleviation of the symptoms of



rheumatoid arthritis, osteoarthritis and pain. Topical NSAIDs can be also used in the treatment of dermatological disorders, such as acne, rosacea, hair growth disorders, actinic keratosis and certain skin cancer conditions.

**[00146]** Immunosuppressant agents, immunoregulating agents and immunomodulators are chemically or biologically-derived agents that modify the immune response or the functioning of the immune system (as by the stimulation of antibody formation or the inhibition of white blood cell activity). Immunosuppressant agents and immunomodulators include, among other options, cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod and imiquimod. Such compounds, delivered in the foam of the present invention, are especially advantageous in skin disorders such as psoriasis, eczema and atopic dermatitis, where the large skin areas are to be treated. The oleaginous foam compositions according to one or more embodiments of the present invention provide excellent vehicles for such applications and are superior to conventional creams and ointments.

#### Topical Anesthetics

**[00147]** Optionally, the compositions according to one or more embodiments of the present invention include an effective amount of a topical anesthetic. The topical anesthetic drug is selected from the group consisting of benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine, phenol, and pharmaceutically acceptable salts thereof. Mixtures of such anesthetic agents may be synergistically beneficial.

**[00148]** The composition according to one or more embodiments of the present invention includes any mixture of synergistically beneficial anesthetic agents.

#### Keratolytically active agents

**[00149]** The term "keratolytically active agent" as used herein, includes but is not limited to a compound, which loosens and removes the stratum corneum of the skin, or alters the structure of the keratin layers of skin.

**[00150]** Keratolytically active 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.

**[00151]** Suitable keratolytically active agents include phenol and substituted phenolic compounds. Such compounds are known to dissolve and loosen the intracellular matrix of the hyperkeratinized tissue. As such, they are used in the treatment of dermatological disorders. Dihydroxy benzene and derivatives thereof have been recognized as potent keratolytic agents. Resorcinol ( m-dihydroxybenzene) and derivatives thereof are used in anti-acne preparations. Hydroquinone (p-dihydroxybenzene), besides hydroquinone anti-pigmentation properties, is also keratolytic. These compounds also exhibit antiseptic properties. Cresols also possess bactericidal and keratolytic properties.

**[00152]** Vitamin A and Vitamin A derivatives, such as retinoic acid, isotretinoic acid, retinol and retinal are another class of keratolytically active agents.

**[00153]** Another group of keratolytically active agents include alpha-hydroxy acids, such as lactic acid and glycolic acid and their respective salts and derivatives; and beta-hydroxy acids, such as salicylic acid (o-hydroxybenzoic acid) and salicylic acid salts and pharmaceutically acceptable derivatives, which typically possess anti-inflammatory, as well as keratolytic, activity.

**[00154]** Yet, another class of keratolytically active agents includes urea and urea derivatives.

#### Retinoids

**[00155]** Another group of active agents includes, for example, retinol, retinal, all trans retinoic acid and derivatives, isomers and analogs thereof, collectively termed "retinoids". Etretinate, actiretin, isotretinoin, adapalene and tazarotene are further examples of retinoid isomers and analogs. Compositions according to one or more embodiments of the present invention including retinoids as the active agent can be used for the treatment of acne, seborrhea, various dermatoses, inflammation of the skin, mucosal membranes, vagina and the rectum, psoriasis, actinic keratosis and skin cancers, by application onto the affected area.

#### Insecticide and Insect repellents agents

**[00156]** Insects, such as mosquitoes, biting flies, mites, gnats, fleas, chiggers, punkies, sand flies, lice and ticks can be annoying and sometimes pose a serious risk to human and animal health. In certain areas of the United States, mosquitoes can transmit diseases like equine and St. Louis encephalitis. Biting flies can inflict a painful bite that can persist for days, swell, and become infected. Ticks can transmit serious diseases like Lyme disease and Rocky Mountain spotted fever.

**[00157]** There are several types of insect repellents to use when protecting people and animals from flying or biting insects, spiders, ticks and mites. Examples of insect repellants include, but are not limited to, DEET (N, N-diethyl-m-toluamide), dimethyl phthalate, piperonyl butoxide and permethrin.

**[00158]** A further example of insect repellents includes the terpenoid compounds, described in U.S. Patent No. 5,411,992, including:

Terpenoid-alcohol or terpene-ols are terpenoids which have at least one hydroxyl group. Examples of terpene-ols include: C<sub>10</sub>H<sub>16</sub>O compounds, perillyl alcohol, carveol, myrtenol, and cis-verbenol; C<sub>10</sub>H<sub>18</sub>O compounds, myrtanol, iso-pinocampheol, dihydrocarveol, isopulegol, terpineol, terpinen-4-ol, nerol, geraniol, and linalool, and C<sub>10</sub>H<sub>20</sub>O compounds, menthol, beta-citronellol, and dihydro-myrcenol.

Terpenoid-esters are terpenoidshaving at least one ester group that is the product of the bonding of the hydroxyl group of a terpene-ol with an aliphatic carboxylic acid that can contain functional groups such as the hydroxyl or amine on the aliphatic chain. Examples of suitable aliphatic carboxylic acids include acetic acid, propionic acid, lactic acid, and various amino acids. Examples of terpenoid-esters include: carvyl acetate, carvyl propionate, and menthyl lactate.

**[00159]** Essential oils and perfumes also contain terpenoids. Non-limiting examples of essential oils having a high content of terpene-ols and esters include bergamot (62% terpenoids); sage (>50% terpenoids); styrax (>50% terpenoids); peppermint (>50% terpenoids); and pine Siberian (75% terpenoids %). Terpenes, aldehydes and ketones vary in their usefulness but as a general group have potential as insect-repellent.

**[00160]** The oleaginous foams according to one or more embodiments of the present invention are particularly suitable for the effective uniform spreading of an insect repellent agent onto large areas of the skin of humans and animals. The hydrophobic solvent present in the foam composition helps retain the insect repellent on the skin surface for an extended period of time.

**[00161]** Yet, in a further embodiment, the oleaginous foams according to one or more embodiments of the present invention are suitable for delivery of insect-killing agents (insecticides) to an afflicted external surface area of humans and animals. Thus, the pharmaceutical or cosmetic composition according to one or more embodiment of the present invention may include an insecticide, known in the art of parasitology. The insecticide is selected from the group consisting of permethrin, hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, malathion, piperonyl

butoxide and any combination thereof at a therapeutically effective concentration. The application of the composition is very convenient and it spreads easily, even over hairy areas. The hydrophobic solvent present in the foam composition helps retain the insecticide on the treated area for an extended period of time. Furthermore, the presence of a hydrophobic solvent in the foam of the present invention eases mechanical removal of lice and nits with a comb.

#### Anti cancer agents

**[00162]** Anti cancer agents can also be used according to one or more embodiments of the present invention in the treatment of skin malignant tumors, such as basal cell carcinoma, squamous cell carcinoma, melanoma and Kaposi's sarcoma, as well as the pre-cancerous condition actinic keratosis. In certain cases, topical cytotoxic and antiproliferative drugs are used to treat or prevent such cancers, including 5-fluorouracil, also called 5-FU. 5-FU, as well as any other anti-cancer agents, known in the art of cancer medicine, can be incorporated in the foam at therapeutically effective levels.

**[00163]** A family of anticancer drugs, suitable for usage in the foam of the present formulation includes anti-estrogens, such as tamoxifen.

#### Photodynamic therapy agents

**[00164]** The foam compositions according to one or more embodiments of the present invention are also useful to deliver photo-sensitizing agents, known in the art of photodynamic therapy. A photosensitizer is selected from the group consisting of porphyrins, chlorins, bacteriochlorins, phthalocyanines, naphthalocyanines, pheophorbides, purpurins, m-THPC, mono-L-aspartyl chlorin e6, bacteriochlorins, phthalocyanines, benzoporphyrin derivatives and photosensitizer precursors, such as aminolevulinic acid (ALA).

#### Active agents for burns, wounds, cuts and ulcers

**[00165]** The treatment of burns, wounds, cuts and ulcers, using the composition according to one or more embodiments of the present invention is particularly advantageous. The oleaginous foam compositions according to one or more embodiments of the present invention may include a combination of anti-infective agents (against bacteria, fungi and/or viruses), anti-inflammatory agents (steroidal and/or

NSAIDs) and pain relieving components. Upon application, the foam spreads easily, covering the surface of the affected area, and without causing pain.

#### Cosmetic active agents

**[00166]** The oleaginous foams according to one or more embodiments of the present invention are useful and advantageous for skin care and cosmetic care. The combination of oil, having refatting, protective and moisture-retaining properties, in a spreadable foam form, can be used to substitute currently used cosmetic skin care creams, lotions, gels, etc. The foam compositions according to one or more embodiments of the present invention, with or without further active ingredients, are suitable for the further application as "cosmeceutical" preparation (cosmetic products with therapeutic benefit), to treat "cosmetic" skin disorders, such as aging skin, wrinkles, hyperpigmentation (melasma, chloasma, freckles, etc.), scaly skin and other skin abnormalities.

**[00167]** The CTFA Cosmetic Ingredient Handbook describes a wide variety of non-limiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry, which are suitable for use in the compositions of the present invention. Examples of these ingredient classes include abrasives, absorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, astringents, etc. (e.g., clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, antifoaming agents, anti-microbial agents (e.g., iodopropyl butylcarbamate), antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers or materials, e.g., polymers, for aiding the film-forming properties and substantivity of the composition (e.g., copolymer of eicosene and vinyl pyrrolidone), opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin bleaching and lightening agents (e.g., hydroquinone, kojic acid, ascorbic acid, magnesium ascorbyl phosphate, ascorbyl glucosamine), skin-conditioning agents (e.g., humectants, including miscellaneous and regulating residence of an active ingredient in the skin), skin soothing and/or healing agents (e.g., panthenol and derivatives (e.g., ethyl panthenol), aloe vera, pantothenic acid and pantothenic acid derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate), skin treating agents, and vitamins and derivatives thereof.

**[00168]** In one embodiment, the active agent is a cosmetic agent selected from the group consisting of: a retinoid, an anti-wrinkle agent, a radical scavenger, a self-tanning agent, a skin whitening agent, a skin protective agent, an anti-cellulite agent, a massaging oil and an anti-wart agent.

Anti-acne and anti-wrinkle active agents

**[00169]** An anti-acne agent is included in the composition according to one or more embodiments of the present invention. The anti-acne agent is selected from the group consisting of: resorcinol, sulfur, salicylic acid and salicylates, alpha-hydroxy acids, nonsteroidal anti-inflammatory agents, benzoyl peroxide, retinoic acid, isotretinoic acid and other retinoid compounds, adapalene, tazarotene, azelaic acid and azelaic acid derivatives, antibiotic agents, such as erythromycin and clindamycin, zinc salts and complexes, and combinations thereof, in a therapeutically effective concentration. Certain anti-acne agents from this list are also useful in the treatment of other skin disease, such as psoriasis, eczema and atopic dermatitis.

Anti-wrinkle active agents/anti-atrophy active agents and agents to treat dry and scaly skin (xerosis and ichthyosis).

**[00170]** Optionally, the compositions according to one or more embodiments of the present invention include a safe and effective amount of at least one anti-wrinkle actives or anti-atrophy active. Exemplary anti-wrinkle/anti-atrophy active agents suitable for use in the compositions according to one or more embodiments of the present invention include sulfur-containing D and L amino acids and their derivatives and salts, particularly the N-acetyl derivatives; thiols; hydroxy acids (e.g., alpha-hydroxy acids such as lactic acid and glycolic acid and their derivatives and salts; or beta-hydroxy acids such as salicylic acid and salicylic acid salts and derivatives), 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). In the case of dry, scaly skin (xerosis) and ichthyosis such agents can alleviate the symptoms by temporary relief of itching associated with these conditions.

### Anti-oxidants/radical scavengers

**[00171]** A safe and effective amount of an anti-oxidant/radical scavenger can be added to the compositions according to one or more embodiments of the present invention, for example, from about 0.1% to about 10%, or from about 1% to about 5% of the composition.

**[00172]** Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and ascorbic acid salts, ascorbyl esters of fatty acids, ascorbic acid derivatives (e.g., magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate), tocopherol (vitamin E), tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename Trolox.sup.R), gallic acid and gallic acid alkyl esters, especially propyl gallate, uric acid and uric acid salts and alkyl esters, sorbic acid and sorbic acid salts, lipoic acid, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g., glutathione), dihydroxy fumaric acid and dihydroxy fumaric acid salts, lysine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and rosemary extracts may be used.

**[00173]** The oleaginous foam according to one or more embodiments of the present invention is suitable for delivering skin protecting and revitalizing anti-oxidants/radical scavengers. Due to the beneficial properties in the treatment of psoriasis and other skin inflammation conditions of specific substances, the composition includes a substance selected from the group consisting of a polyunsaturated fatty acid, containing omega-3 and omega-6 fatty acids (such as linoleic and linolenic acid, gamma-linoleic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Likewise, due to their moisture-retaining and skin protective properties, emollients and silicone oils are included in the composition according to one or more embodiments of the present invention. Thus, in one embodiment, a skin protective foam is provided, wherein the hydrophobic solvent includes in full or in part, a solvent selected from the group consisting of emollients, silicone oil and oils, rich in unsaturated fatty acids, thereby affording a synergistic therapeutic effect of the anti-oxidants/radical scavenger agent and the vehicle components.

### Self-tanning active agents

**[00174]** The oleaginous foams according to one or more embodiments of the present invention are particularly suitable for the uniform delivery of a tanning active agent onto large areas of the skin. The composition includes from about 0.1% to about 20% of dihydroxyacetone or any other compound, known in the art as an artificial tanning active agent.

The composition includes from about 2% to about 7%, or from about 3% to about 6%, of dihydroxyacetone or any other compound, known in the art as an artificial tanning active agent.

#### Solid matter agents

**[00175]** According to one or more embodiments of the present invention, the active agent is a solid matter or particulate matter. Namely the composition includes a at least one active agent which is substantially insoluble in the liquid carrier composition of the foamable composition. For definition purposes, solid matter shall include, but will not be limited to, material substantially insoluble in the foamable composition.

**[00176]** A concentration of at least 10% solid matter is included in the foamable composition. The concentration of the solid matter in the foamable composition is from about 1% to about 20% w/w or from about 2% to about 16% w/w.

**[00177]** By way of example, titanium dioxide, zinc oxide, zirconium oxide, iron oxide and mixtures thereof may be used as solid matter substances. Titanium dioxide has an average primary particle size of from about 15 nm to about 100 nm. Zinc oxide has an average primary particle size of from about 15 nm to about 150 nm. Zirconium oxide has an average primary particle size of from about 15 nm to about 150 nm. Iron oxide has an average primary particle size of from about 15 nm to about 500 nm. In one embodiment the metal oxides are present in the amount of from about 0.1% to about 20%, or from about 0.5% to about 16%, or even from about 1% to about 10%, of the composition. In yet another embodiment, such solids are micronized to form particles having primary size of less than 15 nm.

**[00178]** Other suitable solid materials include silicon-containing solid matter such as silicone oxide, also termed "silica", "fumed silica" and "silica gel", a white or colorless insoluble solid (SiO<sub>2</sub>); and talc, which is fine grained mineral consisting of hydrated magnesium silicate; carbon, for example in the form of amorphous carbon or graphite; oxidizing agents, such as benzoyl peroxide, calcium and magnesium hypochlorite; metallic silver, in small particles, including nanocrystalline silver, which is used for



antibacterial and wound healing purposes; other metal particles and mineral particles; cosmetic scrub materials, including, for example meals of strawberry seeds, raspberry seeds, apricot seeds, sweet almond, cranberry seeds; and pigments, which are insoluble in the foamable composition.

**[00179]** When such solid matter agents are included in the oleaginous foamable composition according to one or more embodiments of the present invention, a foam product combining the refatting, regulating residence of an active ingredient in the skin and protective properties of the oleaginous foam carrier and the beneficial properties of the solid matter agent is afforded.

**[00180]** Generally, products for the prevention and treatment of diaper dermatitis and for skin protection are provided in the form of paste intended for application on the baby's posterior, under the diaper. The paste typically includes about 30% oil and/or petrolatum, and about 10% zinc oxide, which are intended to provide a protective barrier between the baby's skin and the irritating environment inside the diaper. While containing the right ingredients, current baby pastes are very viscous and thick, and therefore hard to spread on the target area.

**[00181]** The oleaginous foam for treating or preventing diaper rash according to one or more embodiments of the present invention includes the following ingredients:

at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof, at a concentration of about 30% to about 90%, preferably between about 30% to about 70%  
water at a concentration of 1% to about 60%;

about 6% to about 20% zinc oxide (or an alternative metal oxide)

at least one non-ionic lipophilic surface active agent, preferably having an HLB value of about 3 to about 10, more preferably about 3.5 to about 9 at a concentration of about 0.1% to about 10%, or between about 0.1% and about 5%;

at least one gelling agent at a concentration of about 0.1% to about 5%;

a liquefied or compressed gas propellant at a concentration of about 3% to about 25% of the total composition, in an aerosol container.

**[00182]** Such foam is superior to current pastes in that it is very fluffy and light. Upon discharge from the aerosol can, it creates a mass, having density between 0.04 gr/mL and 0.2 gr/mL, which is very easy to spread evenly and uniformly on the target area.

There is no need to rub thoroughly and therefore, application of the foam does not cause any discomfort to the baby, unlike conventional baby pastes. Following application and spreading of the foam, a protective layer is formed, which is water resistant, and does not wash out under a stream of tap water.

**[00183]** Foam for diaper dermatitis and/or skin protection can further contain anti-irritant and/or infective agents, such as corticosteroids, anti-inflammatory, anti-allergic, anti-fungal and anti-microbial agents.

#### Skin-Lightening and Whitening Agents

**[00184]** The foam according to one or more embodiments of the present invention is particularly suitable for the uniform delivery of a skin-lightening agent. When used, the compositions may include from about 0.1% to about 10%, or from about 0.2% to about 5%, of the composition, of a skin-lightening agent. Suitable skin lightening or whitening agents include those known in the art, including hydroquinone, azelaic acid and other related dicarboxylic acids, and salts and derivatives thereof, retinoids, kojic acid, arbutin, nicotinic acid and nicotinic acid precursors, salts and derivatives, ascorbic acid and salts and derivatives thereof (e.g., magnesium ascorbyl phosphate or sodium ascorbyl phosphate), and herbal extracts (e.g., mulberry extract, placental extract).

**[00185]** In one or more embodiments of the present invention, the foam composition includes a combination of at least one skin-whitening agent and at least one additional active agent selected from retinoids, keratolytically active agents and anti-inflammatory agents.

**[00186]** In one or more embodiments, the composition includes a combination of at least one skin-whitening agent and at least one keratolytically active agent selected from a alpha-hydroxy acids, beta hydroxy acids, and retinoids.

**[00187]** In one or more embodiments of the present invention, the foam composition includes a combination of a skin-whitening agent and an inorganic sunscreen agent. When inorganic sunscreen agents, e.g. titanium dioxide and zinc oxide, are rubbed onto the skin, they leave a white coating, which provides an instant (although transient) whitening effect, which is highly desirable by the consumer, who wishes to see instant change in his/her appearance. The whitening agent, in combination with the inorganic sunscreen agent in the foam carrier can be easily and uniformly distributed on the skin surface, thereby affording an even instant whitening effect, unlike creams that are difficult to spread evenly on skin areas.

## Sunscreens

[00188] Exposure to ultraviolet light can result in excessive scaling and texture changes of the stratum corneum. The foam composition may be formulated to provide a composition for the delivery of sunscreen agents by inclusion of a sunscreen active. Application of a sunscreen foam is very convenient and it spreads easily over large skin areas. The presence of a hydrophobic solvent in the foam ensures long lasting effect, even while bathing.

[00189] As used herein, "sunscreen active" includes both sunscreen agents and physical sunblocks. Suitable sunscreen actives can be organic or inorganic. Inorganic sunscreens useful herein include metallic oxides such as titanium dioxide having an average primary particle size of from about 15 nm to about 100 nm, zinc oxide having an average primary particle size of from about 15 nm to about 150 nm, zirconium oxide having an average primary particle size of from about 15 nm to about 150 nm, iron oxide having an average primary particle size of from about 15 nm to about 500 nm, and mixtures thereof. When used herein, the inorganic sunscreens are present in the amount of from about 0.1% to about 20% by weight, or from about 0.5% to about 10% by weight, or from about 1% to about 5% by weight.

[00190] A wide variety of conventional organic sunscreen actives are suitable for use herein. Specific suitable sunscreen actives include, for example, p-aminobenzoic acid, p-aminobenzoic acid salts and p-aminobenzoic acid derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-amino-benzoates; 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); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, 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); di-hydroxynaphthoic acid and di-hydroxynaphthoic acid salts; o- and p-hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine 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 tannic acid derivatives (e.g., hexaethylether); (butyl carbotol) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzene, dioxybenzene, benzoescorcinol, 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.

**[00191]** An effective amount of the organic sunscreen active is used, typically from about 1% to about 20% by weight, more typically from about 2% to about 10% by weight of the composition. Exact amounts will vary depending upon the sunscreen or sunscreens chosen and the desired Sun Protection Factor (SPF). A composition containing at least one sunscreen agent having SPF of at least about 15 is useful in protecting the skin from sunburn. In one or more embodiments, a composition containing at least one sunscreen agent having SPF of at least about 15, is useful in preventing a disease comprising skin hyperpigmentation, skin cancer and other skin bioabnormalities, which are associated with excessive exposure to sun. A composition containing at least one sunscreen agent having SPF of at least about 30 can be used.

**[00192]** In one or more embodiments of the present invention, the foam composition includes a combination of a skin-whitening agent and an inorganic sunscreen agent. When inorganic sunscreen agents, e.g. zinc oxide and titanium dioxide, are rubbed onto the skin, they leave a white coating, which provides an immediate (although transient) whitening effect, which is highly desirable by the consumer, who wishes to see instant change in his/her appearance. The whitening agent, in combination with the inorganic sunscreen agent in the foam carrier can be easily and uniformly distributed on the skin surface, thereby affording an even instant whitening effect, unlike creams, which are inherently difficult to spread evenly on skin areas.

Use of a solvent, surface active agent, foam adjuvant and polymeric agent as an active agent.

**[00193]** According to one embodiment, the active agent is selected from the group consisting of a solvent, a surface active agent, a foam adjuvant and a gelling agent, which are, on a case by case basis, known to possess a therapeutic benefit.

## Composition and Foam Physical Characteristics

### Composition flow properties

**[00194]** The composition according to one or more embodiments of the present invention includes water, hydrophobic solvents, formulation excipients and propellant and form a stable emulsion, which has an shelf-life of at least two years at ambient temperature. 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.

**[00195]** The composition according to one or more embodiments of the present invention includes a propellant, e.g., a compressed gas or liquid propellant, which is a low molecular weight hydrocarbon.

**[00196]** Yet, another property of a composition is level of flow of the composition, since a non free flowing composition cannot flow through the dip-tube of the aerosol container and create an acceptable foam. It is known in the art that compositions comprising semi-solid hydrophobic solvents, e.g., white petrolatum, are excessively viscous and demonstrate poor flowability.

**[00197]** According to one or more embodiments of the invention the foamable composition provides a low specific gravity foam having superior expandability, flow properties and sheer breakability (among other attributes). According to one or more embodiments of the present invention, the total amount of at least one surface active agent, at least one foam adjuvant (optional) and at least gelling agent, in combination does not exceed 8 % (w/w) of foamable composition. In other embodiments, the combined amounts of at least one surface active agent, at least one foaming adjuvant and at least one gelling agent is less than 5 % (w/w) of foam composition. The low solid content improves the flow properties of the foam, reduces unpleasant skin residue and reduces the cost of manufacture. As is demonstrated herein, the foam stability and expandability are excellent, despite the low levels of these components in the foam.

### Expandability

**[00198]** Expandability is a further feature of a product that is intended to treat large surface areas and internal cavities of the body. Thus, in one embodiment of the present invention, the specific gravity of the foam, upon discharge from the aerosol can is between about 0.02 gr/mL and 0.5 gr/mL, or between about 0.04 gr/mL and about 0.2 gr/mL.

### Foam Physical Characteristics

**[00199]** An acceptable foam possesses the following consistency and texture characteristics.

**[00200]** Upon release from the aerosol can, a foam mass is created, which is sustained on a surface for at least one minute, preferably at least two minutes and more preferably at least three minutes.

**[00201]** Foam texture should vary from a very fine creamy foam to a fine bubble structure.

**[00202]** The foam has a specific gravity in the range of about 0.02 gr/mL to about 0.5 gr/mL or between about 0.04 gr/mL and about 0.2 gr/mL.

**[00203]** An acceptable foam possesses the following spreadability and absorption characteristics:

The foam does not readily collapse upon dispensing on the skin;

Spreads easily on a skin surface;

Substantially absorbed following rubbing onto the skin.

In terms of organoleptic properties an acceptable foam is one, that:

Creates a pleasant feeling after application;

Leaves minimal oily residue;

Leaves minimal shiny residual look.

**[00204]** The following scale for foam quality is used to evaluate foams:

**E** (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure.

**G** (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam.

**FG** (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable.

**F** (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam.

**P** (poor): no creaminess noticeable, large bubble structure.

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

**[00205]** Foams, adequate for topical administration according to one or more embodiments of the present invention are of quality grade E or G upon release from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container either onto a surface at ambient temperature or onto a skin surface. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

#### Foam stability and breakability

**[00206]** In one or more embodiments, the foam compositions are desirably stable for a long period of time. Thus, the foam composition does not undergo phase separation following at least two freeze/thaw cycles.

**[00207]** According to further embodiments, upon discharge from an aerosol can onto a mucosal membrane at about 37°C, the foam expands to reach the designated volume of the foam and stays stable as a foam for at least 60 seconds following application, or about 2 minutes, or even about 3 minutes.

**[00208]** A further aspect of foam properties, according to one or more embodiments of the present invention is breakability. Sheer-force breakability of the foam, as attained by the composition of the present invention is clearly advantageous to thermally-induced breakability, present, for example in US Pat. 6,126,920 and WO91/11991, and the respective Olux® and Luxiq® products, as demonstrated by the fact that according to the use instructions of Olux® and Luxiq®, the foam cannot be applied on the hand and afterwards delivered to the afflicted area, since it collapses upon exposure to skin temperature.

#### Further technical parameters

**[00209]** The composition according to one or more embodiments of the present invention can be contained in and dispensed from a container capable of withstanding the pressure of the propellant gas and having an appropriate valve/nozzle for dispensing the composition as foam under pressure. A customary liquefied or compressed gas propellant can be added, in the amount of about 3 to about 25% of the total composition. Liquefied propellants are gases that exist as liquids under pressure, including high purity

hydrocarbons such as propane, isobutane and n-butane, dimethyl ether and chlorofluorocarbons (CFCs).

**[00210]** According to one embodiment, the composition of the present invention is placed on a patch, tape or the skin-contact compartment of a transdermal delivery apparatus and applying such object onto the skin, in order to attain effective superficial treatment or enhanced penetration of the drug into the skin or through the skin.

**[00211]** Utilizing such strategy, one can apply drugs, which are currently administered systemically or that require transdermal delivery. Examples for such drugs are nicotine, testosterone and other male hormones and male hormone precursors, estrogen and other female hormones and hormone precursors, growth hormone, insulin, caffeine, steroidal and non-steroidal anti-inflammatory agents and thyroid hormone substitutes.

**[00212]** The therapeutic composition according to the present invention can also be used to prepare cosmetics for beauty purpose by adding into skin care agents and perfume.

#### Metered dosing

**[00213]** In order to provide proper therapy, precise dosing is advantageous. According to one embodiment, the foam therapeutic product is adapted for storage in an aerosol container having a metered dose valve associated therewith for dispensing an accurate dose of drug in the form of a foam. The metered dose valve is selected to release a foam in a volume that will allow effective spreading of the active agent throughout the body surface with substantially minimal overdose.

**[00214]** In one or more embodiments, the meter dose valve provides a unit dose of between about 10  $\mu\text{L}$  and about 1000  $\mu\text{L}$ . Assuming a representative foam density (specific gravity) of 0.06 g/mL, a 10  $\mu\text{L}$  valve provides a volume of about 0.17 mL of foam, and a 1000  $\mu\text{L}$  metered dose valve provides about 17 mL of foam. Thus, by selecting a specific metered dosing valve and adjusting the foam density by fine tuning formulation parameters and adjusting the ration between the liquid components of the composition and the propellant, one can design an adequate dosage form according to the specific target body surface.

#### Fields of Pharmaceutical applications



**[00215]** By including an appropriate therapeutic agent in the foamable carrier, the foam composition according to one or more embodiments of the present invention is useful in treating a patient having any one of a variety of dermatological disorders (also termed "dermatoses"), such as classified, in a non-limiting exemplary manner, according to the following groups:

**[00216]** Dermatitis including Contact Dermatitis, Atopic Dermatitis, Seborrheic Dermatitis, Nummular Dermatitis, Chronic Dermatitis of the hands and feet, Generalized Exfoliative Dermatitis, Stasis Dermatitis; Lichen Simplex Chronicus; Diaper rash; Bacterial Infections including Cellulitis, Acute Lymphangitis, Lymphadenitis, Erysipelas, Cutaneous Abscesses, Necrotizing Subcutaneous Infections, Staphylococcal Scalded Skin Syndrome, Folliculitis, Furuncles, Hidradenitis Suppurativa, Carbuncles, Paronychia Infections, Erythrasma; Fungal Infections including Dermatophyte Infections, Yeast Infections; Parasitic Infections including Scabies, Pediculosis, Creeping Eruption; Viral Infections; Disorders of Hair Follicles and Sebaceous Glands including Acne, Rosacea, Perioral Dermatitis, Hypertrichosis (Hirsutism), Alopecia, including male pattern baldness, alopecia areata, alopecia universalis and alopecia totalis; Pseudofolliculitis Barbae, Keratinous Cyst; Scaling Papular Diseases including Psoriasis, Pityriasis Rosea, Lichen Planus, Pityriasis Rubra Pilaris; Benign Tumors including Moles, Dysplastic Nevi, Skin Tags, Lipomas, Angiomas, Pyogenic Granuloma, Seborrheic Keratoses, Dermatofibroma, Keratoacanthoma, Keloid; Malignant Tumors including Basal Cell Carcinoma, Squamous Cell Carcinoma, Malignant Melanoma, Paget's Disease of the Nipples, Kaposi's Sarcoma; Reactions to Sunlight including Sunburn, Chronic Effects of Sunlight, Photosensitivity; Bullous Diseases including Pemphigus, Bullous Pemphigoid, Dermatitis Herpetiformis, Linear Immunoglobulin A Disease; Pigmentation Disorders including Hypopigmentation such as Vitiligo, Albinism and Postinflammatory hypopigmentation and Hyperpigmentation such as Melasma (chloasma), Drug-induced hyperpigmentation, Postinflammatory hyperpigmentation; Disorders of Cornification including Ichthyosis, Keratosis Pilaris, Calluses and Corns, Actinic keratosis; Pressure Sores; Disorders of Sweating; Inflammatory reactions including Drug Eruptions, Toxic Epidermal Necrolysis; Erythema Multiforme, Erythema Nodosum, Granuloma Annulare.

**[00217]** The oleaginous compositions according to one or more embodiments of the present invention are useful in the therapy of non-dermatological disorders, where in transdermal delivery of an active agent is effective against the, non-dermatological

disorders. By way of example, such disorders include localized pain in general, as well as joint pain, muscle pain, back pain, rheumatic pain, arthritis, osteoarthritis and acute soft tissue injuries and sports injuries. Other disorders of this class include conditions treatable by hormone therapy, such as hormone replacement therapy, transdermal nicotine administration. The foam composition of the present invention is also useful in the delivery of local anesthetic agents.

**[00218]** The oleaginous compositions according to one or more embodiments of the present invention are further useful for the treatment and prevention of disorders and diseases of other body cavities including the rectum, vagina, penile urethra and ear canal.

**[00219]** Thus, the oleaginous foam compositions according to one or more embodiments of the present invention are useful in treating a patient having any one of a variety of gynecological disorders, such as classified, in a non-limiting exemplary manner, according to the following groups:

Pelvic pain, including premenstrual syndrome (PMS), mittelschmerz (severe midcycle pain due to ovulation), dysmenorrhea (pain related to the menstrual cycle), endometriosis, ectopic pregnancy, ovarian cysts and masses, acute pelvic inflammatory disease, pelvic congestion syndrome and vulvodynia; vulvovaginal infections, including bacterial vaginosis, candidal vaginitis, trichomonas vaginalis, herpes simplex genital ulcers and warts, pelvic inflammatory disease (PID), cervicitis, acute and chronic salpingitis; endometriosis; gynecological neoplasms, including endometrial Cancer, ovarian cancer, cervical cancer, vulvar cancer, vaginal cancer, fallopian tube cancer and gestational trophoblastic disease; benign tumors; sexually transmitted diseases; sexual dysfunction disorders that respond to pharmacological therapy, including sexual arousal disorder, female orgasmic disorder, dyspareunia and vaginismus; and various gynecological disorders that respond to hormonal therapy.

**[00220]** The foam according to one or more embodiments of the present invention can be used as a lubricating foam. Without limitation, the lubricating foam is useful in lubrication of the birth canal for easy passage of a newborn baby or the vaginal cavity during intercourse.

**[00221]** Rectal applications include, for example, anal abscess/fistula, anal cancer, anal warts, Crohn's disease, haemorrhoids, anal and perianal pruritus, soreness, and excoriation, perianal thrush, anal fissures, fecal incontinence, constipation, polyps of the colon and rectum.

**[00222]** The oleaginous foam compositions according to one or more embodiments of the present invention are further useful for intra-vaginal and rectal treatment of sexually-transmitted and non-sexually-transmitted infectious disease (STDs).

**[00223]** In one or more embodiments, the invention provides a method of treatment of a disorder of the skin, mucosal membrane, ear channel, vaginal, rectal and penile urethra disorders, comprising topical application of the foam composition of the present invention, whereby one or more active agents, in a therapeutically effective concentration to the afflicted area.

**[00224]** In a further embodiment, the invention provides a method of treatment of a non-dermatological disorder, which responds to topical delivery of an active agent, comprising topical application of the foam composition of the present invention, whereby one or more active agents, in a therapeutically effective concentration to the skin.

#### Treatment / Therapy

**[00225]** The terms "therapy" and "treatment" as used herein interchangeably, cover any treatment of a disease or disorder, and includes, for example:

- (i) curing the disease or disorder;
- (ii) preventing the disease or disorder from occurring in a subject which may

be predisposed to the disease but has not yet been diagnosed as having it;

- (iii) inhibiting the disease or disorder;
- (iv) relieving the disease or disorder;
- (iv) causing regression of the disease;
- (v) providing a beneficial immunological effect;
- (vi) improving the quality of life of a subject afflicted by a disease or disorder;

and, in the case of cosmetic treatment;

(vii) cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions.

**[00226]** In the following, some non-limiting examples and experiments are described in detail. This invention is not limited to these examples and experiments. Many variations will suggest themselves are within the full intended scope of the appended claims.

Example 1 – Anhydrous foam comprising a potent solvent.

**[00227]** The components of the anhydrous foam are listed in the table below.

Ingredient	Synonym	Function	%	%	%	%	%
n-Methyl pyrrolidone	NMP	Potent solvent	68.4	0	0	0	0
Propylene glycol		Potent solvent	0	69.5	0	0	0
Glycofurol		Potent solvent	0	0	69.5		69.5
Dimethyl isosorbide	Arlasolve	Potent solvent	0	0	0	70.0	0
MCT oil	Caprylic/Capric Triglycerides	hydrophobic solvent	9.0	9.0	9.0	9.0	9.0
Hexylene glycol		Co-solvent	2.1	2.1	2.1	2.1	2.1
Glyceryl monostearate		Stabilizer	1.8	1.8	1.8	1.8	1.8
Stearyl alcohol		Stabilizer	1.8	1.8	1.8	1.8	1.8
Oleyl alcohol		Foam adjuvant	2.3	2.3	2.3	2.3	2.3
Sucrose esters	Sucrose esters of fatty acids	Surface active agent	2.0	2.0	2.0	2.0	2.0
Klucel MF	Hydroxypropyl methylcellulose	Gelling agent	0.4	0.4	0.4	0.4	0.4
Preservative			0.3	0.3	0.3	0.3	0.3
Betamethasone valerate		Active agent	0.1	0	0	0	0
Mupirocin		Active agent	0	1.0	0	0	0
Ketoconazole		Active agent	0	0	1.0	0	0
Cyclosporine		Active agent	0	0	0	0.5	0
Acyclovir		Active agent	0	0	0	0	5
Propane/butane		Propellant	12.0	10.0	10.0	10.0	10.0

## Notes:

- The liquefied or gas propellant can be added at a concentration of about 3% to about 25%.
- The compositions used only non-ionic surface active agents, in a concentration of about 2%, and the total amount of surface active agent, foam adjuvants and polymeric agent ranged from about 4% to about 6% (w/w).
- The foam of this example having a density of about 0.2 gr/mL is useful as a carrier of additional active agents. It is also useful as lubricating foam, for various purposes.

Example 2 – MCT oil foams

[00228] The components of the oil/glycerin foam are listed in the table below.

Ingredient	Synonym	Function	%	%	%	%	%	%
Caprylic/Capric Triglycerides	MCT oil	hydrophobic solvent/potent solvent	60.9	60.0	59.0	60.0	60.0	56.0
Propylene glycol		Co-solvent/ potent solvent	10.0	10.0			5.0	5.0
Hexylene glycol		Co-solvent/ potent solvent			10.0	5.0		
Purified water	De-ionized Distilled water	Solvent	10.0	10.0	10.0	10.0	10.0	10.0
Dimethylisorbide						5.0		
PEG 400							5.0	
Glycofurol			--	--	--			5.0
Lecithin	Phospholipids	Surface active agent	10.0	10.0	10.0	10.0	10.0	10.0
Stearyl alcohol		Stabilizer	5.0	5.0	5.0	5.0	5.0	5.0
Glyceryl monostearate		Stabilizer	2.0	2.0	2.0	2.0	2.0	2.0
PVP K90	Polyvinyl pyrrolidone	Gelling agent	2.0	2.0	2.0	2.0	2.0	2.0
Preservative			0.3	0.3	0.3	0.3	0.3	0.3
Betamethasone valerate		Active agent	0.1					
Mupirocin		Active agent		1.0			1.0	
Ketoconazole		Active agent			2.0			
Tacrolimus		Active agent				1.0		
Acyclovir		Active agent						5.0
Propane/butane		Propellant	12.0	10.0	10.0	10.0	10.0	10.0

Notes:

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

- The potent solvent and hexylene glycol (emollient) may be optionally incorporated.
- In these particular examples, a minimal water content was used for the gelling agent incorporation; higher levels of water are an option.
- Lecithin is provided as the surface active agent. Several types of powdered, de-oiled and liquid (55% to 80% Phosphatidyl choline) phospholids have been tested successfully for the production of acceptable foams.
- In the current examples, polyvinylpyrrolidone (PVP) was used as the gelling agent; however, other gelling agents can be used as well.
- The compositions use only non-ionic surface active agents, in concentration of about 2%, and the total amount of surface active agent, foam adjuvants and polymeric agent ranged from about 4% to about 6% (w/w).
- The foam of this example is useful as a carrier of additional active agents. It is also useful as lubricating foam, for various purposes.
- Stearyl alcohol, cetyl alcohol or oleyl alcohol (foam adjuvants) and co-solvents, such as propylene glycol and hexylene glycol, are optionally incorporated in the foam.
- Density of the foam is about 0.08 to about 0.40 gr/mL.

Example 3 – MCT Foam with no gelling agent

	% w/w
MCT oil	52.78
Glyceryl monostearate NE	1.85
Stearyl alcohol	4.35
Polyoxyethylene (2) Stearyl Ether	2.78
PPG-15 stearyl ether	0.93
Span 60	1.85
Lecithin de-oiled	9.26
Hexilene glycol	9.26
Water pur.	9.26
Preservative	0.28
Propellant	7.41
Foam	E
Foam density	0.10



Example 3: Oil/glycerin foam

[00229] The components of the oil/glycerin foam are listed in the table below.

Ingredient	Synonym	Function	%	%	%	%
Glycerin	Glycerol	Co-solvent	32.0	32.0	32.5	40.5
Purified water		Solvent	17.0	17.0	18.55	14.05
MCT oil	Caprylic/Capric Triglycerides	Hydrophobic Solvent	9.0	9.0	9.0	8.0
Isopropyl myristate	IPM	Co-solvent	0	0	9.0	8.0
Isopropyl palmitate	IPP	Co-solvent	0	10.0	0	0
Diisopropyl adipate	DISPA	Co-solvent	9.0	0	0	0
Hexylene glycol	Hexylene glycol	Emollient	9.0	9.0	9.0	8.0
Oleyl alcohol	Oleyl alcohol	Foam adjuvant	9.0	9.0	9.0	8.0
Sisterna sp-50	Sucrose ester	Surface active agent	1.8	1.8	1.8	1.8
Glyceryl monostearate	Glyceryl monostearate	Stabilizer	0.4	0.4	0.4	0.4
Pemulen TR2	Acrylates/C10-30 Alkyl Acrylate Cross-Polymer	Stabilizer	0.1	0.1	0.1	0.1
Methocel K100M	Methyl cellulose	Gelling agent	0.3	0.3	0.3	0.3
TEA	Tri-ethanolamine	Neutralizer	0.05	0.05	0.05	0.05
Phenonip	Methyl, butyl, propyl paraben, phenoxyethanol	Preservative	0.25	0.35	0.3	0.3
Betamethasone valerate		Active agent	0.1	0	0	0
Mupirocin		Active agent	0	1.0	0	0
Ketoconazole		Active agent	0	0	2.0	0
Cyclosporine		Active agent	0	0	0	0.5
Propane/butane		Propellant	12.0	10.0	8.0	10.0

Notes:

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

- In non-limiting examples, the oil/glycerin foams of the present invention contain about 10% to about 20% water, about 37% glycerin and about 30% oil blend and about 10% hexylene glycol.
- The compositions use only non-ionic surface active agents, in concentration of about 2%, and the total amount of surface active agent, foam adjuvants and polymeric agent ranged from about 8% to about 12% (w/w).
- The foam of this example is useful as a carrier of additional active agents. It is also useful as lubricating foam, for various purposes.
- Density of the foam is about 0.18 gr/mL to about 0.20 gr/mL.
- Upon release from the aerosol can, foam is released, and stays stable for several minutes, until it is rubbed onto the afflicted area, then it is immediately broken down and absorbed. This property enables convenient and even application with good sensory feeling.

#### Example 4: Compositions comprising PEG

**[00230]** Compositions comprising polyethylene glycol (PEG) derivatives have been prepared and shown to be excellent foams. According to the following non-limiting example the composition comprises about 80% to about 97.5% PEG 400, about 1% to about 5% of at least one surface active agent having HLB between 2 and 9 and 0.5% gelling agent, prior to the addition of a propellant (about 10% of the total composition). Notably the following compositions did not comprise any water at all.

Example 5. PEG 400 foamable compositions (Vehicle)

	%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.

**[00231]** The following table exemplifies the use of PEG 400 as a potent 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 400 as the sole solvent is highly valuable.

Example 6. - PEG foamable compositions, comprising Mupirocin

	% 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
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 7 – PEG foamable composition with no surfactant

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

Example 6. Comparison between PEG 400 foamable compositions with and without gelling agent.

**[00232]** 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 gelling agent, 100% breakdown occurred within 30 seconds, while foams containing gelling agent remained, with and without surfactant, were stable for several minutes.

	Formulations without gelling agent				Formulation with gelling agent	
	PG33	PG34	PG35	PG36	TEC49	PG29
:	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
PEG 400	87.25	93.00	91.00	92.00	90.50	93.50
Klucel GF	---	---	---	---	0.50	0.50
Cetareth-15	---	---	2.00	1.00	---	---
Emulsifying Wax NF	1.80	---	---	---	---	---
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 (38°C; Seconds)	<30	<30	<30	<30	240	>300

What is claimed is:

## CLAIMS

1. An oleaginous foamable therapeutic composition, comprising:
  - a. a solvent selected from the group consisting of a hydrophobic solvent, a silicone oil, an emollient, a co-solvent, and mixtures thereof, wherein said solvent is present at a concentration of about 70% to about 96.5% by weight of the total composition;
  - b. a surface-active agent at a concentration of about 0.1% to about 10% by weight of the total composition;
  - c. a therapeutically effective amount of an active agent;
  - d. a propellant at a concentration of about 3% to about 25% by weight of the total composition.
2. The oleaginous foamable therapeutic composition of claim 1, further comprising a gelling agent at a concentration of about 0.1% to about 5% by weight of the total composition.
3. The oleaginous foamable therapeutic composition of claim 1, further comprising a foam adjuvant selected from the group consisting of a fatty alcohol having at least 15 carbon atoms and a fatty acid having at least 16 carbon atoms.
4. The oleaginous foamable therapeutic composition of claim 1, wherein said solvent comprises a hydrophobic solvent having a degree of solubility of less than about one gram of solvent per 100 ml of distilled water at ambient temperature.
5. The oleaginous foamable therapeutic composition of claim 1, wherein said solvent comprises a hydrophobic solvent selected from the group consisting of a mineral oil, a triglyceride oil, a silicone oil, a polyunsaturated oil, an unsaturated oil and an essential oil.
6. The oleaginous foamable therapeutic composition of claim 1, wherein said solvent comprises a mixture of at least one hydrophobic solvent and at least one co-solvent.

7. The oleaginous foamable therapeutic composition of claim 1, wherein said solvent includes a mixture of a hydrophobic solvent and a co-solvent in a weight ratio of about 1:8 to about 8:1 said hydrophobic solvent to said co-solvent.

8. The oleaginous foamable therapeutic composition of claim 1, wherein said co-solvent is selected from the group consisting of polyols, sulfoxides, oleates, lactam compounds, esters, amides, alkanolic acids, and alkanols and admixtures thereof.

9. The oleaginous foamable therapeutic composition of claim 6, wherein said mixture forms an emulsion.

10. The oleaginous foamable therapeutic composition of claim 6, wherein said co-solvent comprises glycerin.

11. The oleaginous foamable therapeutic composition of claim 10, wherein said mixture of at least one hydrophobic solvent and glycerin comprises a weight ratio of about 1:4 to about 4:1.

12. The oleaginous foamable therapeutic composition of claim 10, wherein said mixture of at least one hydrophobic solvent and glycerin comprises a weight ratio of about 1:2 to about 2:1.

13. The oleaginous foamable therapeutic composition of claims 1 or 6, wherein said co-solvent comprises a polyethylene glycol.

14. The oleaginous foamable therapeutic composition of claim 1, wherein the said solvent comprises a potent solvent.

15. The oleaginous foamable therapeutic composition of claim 14, wherein said potent solvent solubilizes the active agent at a degree at least 5 times greater than the degree that mineral oil solubilizes the active agent.

16. The oleaginous foamable therapeutic composition of claim 14, wherein said potent solvent solubilizes the active agent at a degree at least 10 times greater than the degree that mineral oil solubilizes the active agent.

17. The oleaginous foamable therapeutic composition of claim 14, wherein said potent solvent is selected from the group consisting of a polyol, polyethylene glycol, propylene glycol, hexylene glycol, butanediols and isomers thereof, glycerol, benzyl alcohol, DMSO, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, dimethyl isosorbide, glycofurool and ethoxydiglycol (transcutol) and mixture thereof in any proportion.

18. The oleaginous foamable therapeutic composition of claim 15 or 16, wherein said potent solvent is a polyol and said active agent is mupirocin.

19. The oleaginous foamable therapeutic composition of claim 14, wherein said polyol is a liquid polyethylene glycol.

20. The oleaginous foamable therapeutic composition of claim 1, wherein, said surface active agent comprises at least one non-ionic surface active agent.

21. The oleaginous foamable therapeutic composition of claim 20, further comprising an ionic surface-active agent.

22. The oleaginous foamable therapeutic composition of claim 21, wherein said non-ionic surface-active agent and said ionic surface-active agent are present at a weight ratio of about 20:1 to about 1:1 non-ionic surface active agent to ionic surface active agent.

23. The oleaginous foamable therapeutic composition of claim 1, wherein the concentration of said surface-active agent is less than about 2% of the entire composition.

24. The oleaginous foamable therapeutic composition of claim 1, wherein the surface-active agent comprises a phospholipid.

25. The oleaginous foamable therapeutic composition of claim 24, wherein the phospholipid comprises phosphatidylcholine.



26. The oleaginous foamable therapeutic composition of claim 2, wherein said gelling agent is selected from the group consisting of a natural polymeric material, a semi-synthetic polymeric material, a synthetic polymeric material, an inorganic gelling agent and any mixture thereof.

27. The oleaginous foamable therapeutic composition of claim 1, wherein oleaginous foamable therapeutic composition includes less than about 20% by weight of water.

28. The oleaginous foamable therapeutic composition of claim 27, having a specific gravity of about 0.01 gr/ml to about 0.4 gr/mL upon release from said pressurized container.

29. The oleaginous foamable therapeutic composition of claim 1, wherein said active agent is selected to treat a dermatological or mucosal disorder.

30. The oleaginous foamable therapeutic composition of claim 29, wherein said disorder is selected from the group consisting of a bacterial disorder, a fungal disorder, a viral disorder, a parasitic disorder, an inflammatory disorder, an autoimmune disorder, an allergic disorder, a hormonal disorder, a malignant disorder, a cosmetic abnormality and any combination thereof.

31. The oleaginous foamable therapeutic composition of claim 1, wherein the active agent is a component of the foamable composition selected from the group consisting of a solvent, a surface-active agent, a gelling agent and a foam adjuvant.

32. The oleaginous foamable therapeutic composition of claim 29, wherein said therapeutic agent is selected from the group consisting of an anti-infective, an antibiotic, an antibacterial agent, an antifungal agent, an antiviral agent, an antiparasitic agent, an antiinflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K,

a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an analgesic, an antiallergic agent, a corticosteroid, a non-steroidal anti-inflammatory drug, an alpha hydroxyl acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, a allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, an anti-wrinkle agent, a radical scavenger, a self-tanning agent, a skin whitening agent, a skin protective agent, an anti-cellulite agent, a massaging oil and an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

33. The oleaginous foamable therapeutic composition of claim 29, wherein the therapeutic agent is selected for the treatment of a disorder of the skin, mucosal membrane, ear channel, vagina, penile urethra, colon and rectum.

34. The oleaginous foamable therapeutic composition of claim 29, wherein the cosmetic agent is selected from the group consisting of a retinoid, an anti-wrinkle agent, a radical scavenger, a self-tanning agent, a skin whitening agent, a skin protective agent, an anti-cellulite agent, a massaging oil and an anti-wart agent.

35. The oleaginous composition of claim 1, wherein the therapeutic agent is intended for transdermal delivery.

36. The oleaginous foamable therapeutic composition of claim 1, wherein the active agent comprises an inorganic solid matter

37. The oleaginous foamable therapeutic composition of claim 36, wherein the inorganic solid matter comprises a metal oxide selected to form a protective layer on a body surface or a mucosal membrane.

38. A stable oleaginous foamable water-in-oil emulsion, comprising

- a. a solvent selected from the group consisting of a hydrophobic solvent, a co-solvent and an emollient at a concentration of about 30% to about 96.5% by weight;
- b. water;

- c. a lipophilic surface-active agent having an HLB value of about 3 to about 10 at a concentration of about 0.1 % to less than about 10% by weight,
- d. a therapeutically effective amount of an active agent; and
- e. a propellant at a concentration of about 3% to about 25% by weight of the total composition.

39. The oleaginous foamable water-in-oil emulsion of claim 38, further comprising a gelling agent at a concentration of about 0.1% to about 5% by weight of the total composition.

40. The oleaginous foamable water-in-oil emulsion of claim 38, further comprising a foam adjuvant selected from the group consisting of fatty alcohols having greater than or equal to 15 carbons and fatty acids having greater than or equal to 16 carbons.

41. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the solvent comprises a hydrophobic solvent having solubility in distilled water at ambient temperature of less than about one gram per 100 ml.

42. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the hydrophobic solvent is selected from the group consisting of mineral oil, a triglyceride oil, an ester of a fatty acid, an ester of a dicarboxylic acid, a silicone oil, a polyunsaturated oil, an unsaturated oil and an essential oil.

43. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the hydrophobic solvent and water are present at a weight ratio in the range of about 1:3 to about 6:1.

44. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the solvent comprises a potent solvent selected from the group consisting of hydrophobic solvents other than mineral oil, wherein the potent solvent solubilizes an active agent substantially better than mineral oil solubilizes the active agent.

45. The oleaginous foamable water-in-oil emulsion of claim 44, wherein the potent solvent solubilizes the active agent at least 5-fold better than mineral oil solubilizes the active agent.

46. The oleaginous foamable water-in-oil emulsion of claim 44, wherein said potent solvent solubilizes the active agent at least 10-fold better than a mineral oil solubilizes the active agent.

47. The oleaginous foamable water-in-oil emulsion of claim 44, wherein the potent solvent is selected from the group consisting of polyols, polyethylene glycols, propylene glycols, hexylene glycols, butanediols and isomers thereof, glycerols, benzyl alcohol, DMSO, ethyl oleates, ethyl caprylates, diisopropyl adipate, dimethylacetamides, N-methylpyrrolidones, N-hydroxyethylpyrrolidones, polyvinylpyrrolidones, an isosorbide derivatives, glycofurols and ethoxydiglycols (transcutol) and mixtures thereof in any proportion.

48. The oleaginous foamable therapeutic composition of claim 38, wherein, said surface active agent comprises at least one non-ionic surface active agent.

49. The oleaginous foamable therapeutic composition of claim 48, further comprising an ionic surface-active agent.

50. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the concentration of the surface-active agent is less than about 2%.

51. The oleaginous foamable water-in-oil emulsion of claim 48, wherein said surface-active agent is selected from the group consisting of sorbitan derivatives; alkoxyated alcohols; hydroxylated derivatives of polymeric silicones; alkylated derivatives of hydroxylated polymeric silicones; glyceryl esters; beeswax derivatives; lecithin; and mixtures thereof.

52. The oleaginous foamable water-in-oil emulsion of claim 38, wherein said co-solvent is selected from the group consisting of polyols, sulfoxides, oleates, lactam compounds, esters, amides, alkanolic acids, and alkanols and admixtures thereof.

53. The oleaginous foamable water-in-oil emulsion of claim 39, wherein the gelling agent is selected from the group consisting of natural polymeric materials, semi-synthetic polymeric materials, synthetic polymeric materials, inorganic gelling agents and mixtures thereof.

54. The oleaginous foamable water-in-oil emulsion of claim 53, wherein the inorganic gelling agent comprises silicone dioxide.

55. The oleaginous foamable water-in-oil emulsion of claim 38, having a specific gravity of about 0.01 gr/ml to about 0.4 gr/mL, upon extrusion from a pressured container.

56. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the active agent is a component of the foamable composition and is selected from the group consisting of a solvent, a surface-active agent, a gelling agent and a foam adjuvant.

57. The oleaginous foamable water-in-oil emulsion of claim 38 wherein the active agent is selected from the group consisting of an anti-infective, an antibiotic, an antibacterial agent, an antifungal agent, an antiviral agent, an antiparasitic agent, an antiinflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an analgesic, an antiallergic agent, a corticosteroid, a non-steroidal anti-inflammatory drug, an alpha hydroxyl acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a

retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, an anti-wrinkle agent, a radical scavenger, a self-tanning agent, a skin whitening agent, a skin protective agent, an anti-cellulite agent, a massaging oil and an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

58. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the therapeutic agent is selected for the treatment of a disorder of the skin, mucosal membrane, ear channel, vagina, penile urethra and rectum.

59. The oleaginous foamable water-in-oil emulsion of claim 38, wherein the etiology of the dermatological or mucosal disorder is bacterial, fungal, viral, parasitic, inflammatory, autoimmune, allergic, hormonal, malignant and combinations thereof.

60. The oleaginous foamable water-in-oil emulsion of claim 38, wherein active agent is an inorganic solid matter.

61. The oleaginous foamable water-in-oil emulsion of claim 60, wherein the inorganic solid matter is selected to form a protective layer on a body surface, a body cavity or a mucosal membrane.

62. The oleaginous foamable water-in-oil emulsion of claim 61, wherein the inorganic solid matter is selected to treat a skin disorder selected from sensitive skin, diaper rash and diaper dermatitis.

63. An oleaginous foam for treating or preventing diaper rash comprising  
at least one solvent selected from the group consisting of a hydrophobic solvent, a co-solvent, an emollient and mixtures thereof, at a concentration of about 30% to about 90%, preferably between about 30% to about 70%  
water at a concentration of 1% to about 60%;  
about 6% to about 20% metal oxide)  
at least one non-ionic lipophilic surface active agent, having an HLB value of about 3 to about 10,  
at least one gelling agent at a concentration of about 0.1% to about 5%;

a propellant at a concentration of about 3% to about 25% of the total composition

wherein said composition is contained in an aerosol container.

64. The oleaginous foamable water-in-oil emulsion of claim 63, wherein the concentration of said solvent is about 30% to about 70% .

65. The oleaginous foamable water-in-oil emulsion of claim 63, wherein the concentration of said metal oxide is zinc oxide .

66. The oleaginous foamable water-in-oil emulsion of claim 63, wherein the concentration of said surface active agent has an HLB value of about 3.5 to about 9.

67. The oleaginous foamable water-in-oil emulsion of claim 63, wherein the concentration of said surface active agent is about 0.1% to about 10%.

68. The oleaginous foamable water-in-oil emulsion of claim 63, wherein the concentration of said surface active agent at a concentration of about 0.1% to about 5%;

69. An oleaginous foamable therapeutic composition comprising at least one active ingredient, at least one solvent, wherein the degree of active ingredient solubilization by said potent solvent is greater than the degree of said at least one active agent solubilization by a mineral oil, and a gelling agent.

70. The oleaginous foamable composition of claim 69, wherein the potent solvent comprises a polyol or a mixture of polyols.

71. The oleaginous foamable composition of claim 69, wherein said polyol is flowable at ambient temperature.

72. The oleaginous foamable composition of claim 69, wherein said polyol has a viscosity of less than about 20,000 cps at ambient temperature.

73. The oleaginous foamable composition of claim 69, wherein said polyol has a viscosity of less than about 10,000 cps at ambient temperature.

74. The oleaginous foamable composition of claim 69, where the gelling agent comprises a polysaccharide

75. The oleaginous foamable composition of claim 74, where said polysaccharide hydroxypropylcellulose.

76. The oleaginous foamable water-in-oil emulsion of claim 1, 38, 63 and 69 comprising less than about 5% of a short chain alcohols having up to 5 carbon atoms in the short chain alcohol carbon chain.

77. A method of treating, alleviating or preventing a dermatological, cosmetic or mucosal disorder, comprising administering topically to a subject having said disorder a therapeutically effective amount of an oleaginous foam composition according to any of claims 1 through 75.

78. A method of designing a foamable composition, comprising at least one active agent that is substantially insoluble in mineral oil, comprising the steps of:

- i. selecting at least one active agent;
- ii. identifying a potent solvent that solubilizes said at least one active agent substantially better than mineral oil solubilizes said at least one active agent, whereby the active agent is solubilized in the composition; and
- iii. adjusting the type and concentration of surface active agent and gelling agent, to provide a foamable composition

79. The method of claim 77, wherein the potent solvent solubilizes the active agent 5 fold better than a hydrocarbon solvent solubilizes the active agent.

80. The method of claim 77, wherein the potent solvent solubilizes the active agent 10 fold better than a hydrocarbon solvent solubilizes the active agent.

81. An oleaginous foamable therapeutic composition, essentially free of alcohol, comprising:



- a. a solvent selected from the group consisting of: a hydrophobic solvent, 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;
- b. a surface-active agent at a concentration of about 0.1% to about 25% by weight of the total composition, wherein the surface-active agent comprises a phospholipid;
- c. a gelling agent at a concentration of about 0.1% to about 5% by weight of the total composition;
- d. a therapeutically effective amount of an active agent;
- e. a propellant at a concentration of about 3% to about 25% by weight of the total composition.

82. The composition of claim 81, wherein the phospholipid comprises lethicin.

83. The oleaginous foamable therapeutic composition of claim 81, wherein, said surface active agent comprises at least one non-ionic surface active agent

84. The oleaginous foamable therapeutic composition of claim 81, further comprising an ionic surface-active agent.

85. A therapeutic device, comprising a pressurized can, equipped with a metered dose valve and an actuator capable of dispensing a foam, and containing an oleaginous foam composition according to any of claims 1 through 75 and 81 through 84.

86. The device of claim 85, wherein the metered dose valve provides a unit dose of between about 10  $\mu\text{L}$  and about 1000  $\mu\text{L}$ .

87. The device of claim 85, wherein the metered dose valve provides a unit dose of between about 50  $\mu\text{L}$  and about 250  $\mu\text{L}$ .

88. A kit comprising a packaging material and contained therein an oleaginous foamable pharmaceutical composition in a container comprising at least one active ingredient, at least one solvent, a gelling agent, and a propellant, said gelling agent being capable of thickening the composition;

said propellant capable of forming a foam upon release of the composition from the containing; and

said packaging material comprising a label which indicates that said pharmaceutical composition can be used for the treatment of a given superficial disorder, which preferably responds to treatment by said active agent, delivered in an oleaginous vehicle, in a therapeutically effective dose.