Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2769677 A1 2011/02/03

(21) 2 769 677

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2010/07/29
(87) Date publication PCT/PCT Publication Date: 2011/02/03
(85) Entrée phase nationale/National Entry: 2012/01/30
(86) N° demande PCT/PCT Application No.: IB 2010/002238
(87) N° publication PCT/PCT Publication No.: 2011/013008
(30) Priorité/Priority: 2009/07/29 (US61/229,338)

(51) Cl.Int./Int.Cl. *B01F 17/38* (2006.01), *A01N 25/16* (2006.01), *A61K 47/30* (2006.01)

(71) Demandeur/Applicant:
FOAMIX LTD., IL

(72) Inventeurs/Inventors:
TAMARKIN, DOV, IL;
ZIV, ENBAL, IL;
HAZOT, YOHAN, IL;
SCHUZ, DAVID, IL

(74) Agent: CASSAN MACLEAN

(54) Titre : COMPOSITIONS HYDRO-ALCOOLIQUES MOUSSANTES A BASE D'AGENTS NON TENSIOACTIFS NON POLYMERES, MOUSSES LEGERES, ET LEURS UTILISATIONS

(54) Title: NON SURFACE ACTIVE AGENT NON POLYMERIC AGENT HYDRO-ALCOHOLIC FOAMABLE COMPOSITIONS, BREAKABLE FOAMS AND THEIR USES

(57) Abrégé/Abstract:
A substantially surface active agent- free and substantially polymeric agent- free foamable composition which includes short-chain alcohol, water, fatty alcohol or fatty acid or a combination of fatty alcohol and fatty acid and propellant. A substantially surface active agent- free and substantially polymeric agent-free foamable composition which includes water, fatty alcohol or fatty acid and propellant. A method of treatment using a substantially surface active agent- free and substantially polymeric agent- free foamable composition.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2011 (03.02.2011)

PCT

(10) International Publication Number
WO 2011/013008 A4

(51) International Patent Classification:
C11D 7/22 (2006.01)

(21) International Application Number:
PCT/IB2010/002238

(22) International Filing Date:
29 July 2010 (29.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/229,338 29 July 2009 (29.07.2009) US

(71) Applicant *(for all designated States except US)*: **FOAMIX LTD.** [IL/IL]; PO Box 4038, 74140 Ness Ziona (IL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TAMARKIN, Dov** [IL/IL]; 537 Har Hila Street, 71908 Ness Ziona (IL). **ZIV, Enbal** [IL/IL]; Perhay Bar, 6/9, 74140 Gedera (IL). **HAZOT, Yohan** [IL/IL]; Rahavat Ilan 22B/1, Givat Shmuel (IL). **SCHUZ, David** [IL/IL]; PO Box 4038, 74140 Ness Ziona (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

(88) Date of publication of the international search report:
12 May 2011

Date of publication of the amended claims and statement: 14 July 2011

WO 2011/013008 A4

(54) Title: NON SURFACE ACTIVE AGENT NON POLYMERIC AGENT HYDRO-ALCOHOLIC FOAMABLE COMPOSITIONS, BREAKABLE FOAMS AND THEIR USES

(57) Abstract: A substantially surface active agent- free and substantially polymeric agent- free foamable composition which includes short-chain alcohol, water, fatty alcohol or fatty acid or a combination of fatty alcohol and fatty acid and propellant. A substantially surface active agent- free and substantially polymeric agent-free foamable composition which includes water, fatty alcohol or fatty acid and propellant. A method of treatment using a substantially surface active agent- free and substantially polymeric agent- free foamable composition.

NON SURFACE ACTIVE AGENT NON POLYMERIC AGENT HYDRO-ALCOHOLIC FOAMABLE COMPOSITIONS, BREAKABLE FOAMS AND THEIR USES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. §119(e) to co-pending U.S. Patent Application No. 61/229338 filed on July 29, 2009, entitled "NON SURFACE ACTIVE AGENT NON POLYMERIC AGENT HYDRO-ALCOHOLIC FORMABLE COMPOSITIONS, BREAKABLE FOAMS AND THEIR USES," which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Foam compositions with high amounts of alcohol are known in the art. Alcohol-based compositions are useful because of the anti-microbial properties of alcohol and the ability for alcohol to dissolve certain active agents.

[0003] Foams and, in particular, single-phase foams are complicated systems which do not form under all circumstances. Slight shifts in foam composition, such as by the addition of active ingredients or the removal of any of the essential ingredients, may destabilize the foam.

[0004] The prior art teaches hydro-alcoholic foam compositions require significant amounts of short-chain alcohols (namely, ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol and pentanol), water, fatty alcohols, polymer and surfactant to form a foam. These compositions require various surfactants, such as, non-ionic surfactants, anionic, cationic, zwitterionic, amphoteric and ampholytic surfactants, as essential components.

[0005] Surfactants are known as essential ingredients in foam compositions because of their amphiphilic properties and because they are considered essential in forming a foam. However, many surfactants are known to be irritating when left on

the skin, as they can extract lipids from the skin, thereby damaging skin barrier and exposing the skin to contact with pro-inflammatory factors. (*See, Dermatitis,* Vol. 33(4) 217-225, 11 Apr 2006, John Wiley & Sons).

[0006] Lower alcohols are defatting agents. They are known to extract skin fats, thereby disrupting skin barrier function and causing irritation. They are known to cause skin to become dry and cracked (*See, for example, Industrial Guide to Chemical and Drug Safety*, by T. S. S. Dikshith, Prakash V. Diwan, John Wiley & Sons, Inc., 2003, p. 228-9).

[0007] Thus the combination of a short chain alcohol and a surfactant can have a doubly undesirable irritating and defatting effect, as well as the drawback of enhanced delivery of drugs through the skin, which results in increased systemic exposure (which is undesirable for topical treatment of the skin).

[0008] Hydro-alcoholic foams, as described in the prior art are inherently thermally unstable, and they will collapse upon exposure to the skin and body (at temperatures around 37°C). They are therefore commonly termed "quick breaking" foams. Typically, when a quick breaking foam is applied to fingers (as is usually done in order to apply a drug to a target area), it melts and rapidly (on exposure to body temperature of about 37°C) and collapses leaving behind a small pool of liquid. The thermal instability of the foam makes it difficult to apply to a large target area by first administering the foam to the hands and then spreading the foam onto the affected area.

SUMMARY

[0009] The present application relates to foamable formulations and foams and their uses comprising, short chain alcohols ("SCA's"), and especially ethanol. In one or more embodiments the short chain alcohol is isopropanol. In one or more embodiments the SCA's are needed as part of a drug carrier. For example certain drugs require alcohol in order to solubilize them. In one or more other embodiments, the SCA's are provided to facilitate or enhance the transdermal penetration or delivery of a drug. In one or more additional cases, the SCA's are

provided to have a defatting effect at the target site, for example where the site of treatment is oily and the defatting effect of alcohol is desirable.

[0010] Unexpectedly, it has been discovered that quality hydro-alcoholic foamable formulations and foams can be achieved which upon dispensing are thermally stable, for example, for at least 60 seconds at 36°C, yet easily breakable upon application of shear force, without the presence of significant amounts of standard surface active agents known in the art. In other words contrary to the prior art these foams do not collapse rapidly on exposure to body temperature but remain stable for a sufficient period of time so that they can be conveniently applied to a target site without having to take special precautions, such as only applying the foam to a cold surface. Also, surprisingly they can form quality foamable formulations and foams even in the absence of customary polymeric agents. Thus, in one or more embodiments, there is provided a substantially surfactant free hydro-alcoholic foamable formulation or foam. In one or more preferred embodiments the hydro-alcoholic formulations and foams are free of surface active agents. Thus, in one or more embodiments, there is also provided a substantially polymeric agent free hydro-alcoholic foamable formulation or foam. In one or more preferred embodiments the hydro-alcoholic formulations and foams are free of surfactants and polymeric agents. Moreover, it has been further discovered that these formulations and foams can be achieved over a large range of alcohol content. Thus, for certain delivery systems there is provided a surfactant-free foamable and or polymeric agent free composition and foam, comprising about a medium level to about a very high level of content of a short-chain alcohol.

[0011] In one or more embodiments there is provided a safe and effective foamable carrier composition and foam comprising a short chain alcohol ("SCA"), water, a foaming booster and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition, wherein the percent by weight is based on weight foamable composition; wherein the ratio of composition other than propellant to propellant is from about 100:3 to about 100:30. In one or more other embodiments there is provided a safe and effective foamable pharmaceutical or cosmetic composition and foam comprising an effective amount

of a pharmaceutical or cosmetic agent, a short chain alcohol ("SCA"), water, a foaming booster and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition wherein the percent by weight is based on weight foamable composition; wherein the ratio of composition other than propellant to propellant is from about 100:3 to about 100:30. The foaming booster surprisingly does not need to include a surfactant; and can include at least one fatty alcohol or one or at least one fatty acid or a combination thereof or a synergistic combination of two or more fatty alcohols. The SCA is present in a substantial amount. By a substantial amount is meant that the alcohol is present at a % concentration by weight at which it is capable of having a defoaming effect and/or an irritating effect. In one or more embodiments the alcohol is at least about 15% by weight. In other embodiments it is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, or at least about 60% by weight. In one or more embodiments the SCA is at a concentration between about 15% to about 65% by weight, or about 20% to about 60% by weight, preferably between about 25% to about 55% by weight, and more preferably between about 30% to about 50% by weight. The carrier and pharmaceutical composition is substantially surfactant free and preferably does not contain a surfactant.

[0012] In one or more embodiments there is provided a substantially surfactant free and polymeric agent free foamable composition comprising a short chain alcohol, water, a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof and liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition. The percent by weight is based on weight foamable composition; wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and wherein upon dispensing the foamable carrier composition forms a foam of quality that is thermally stable at a temperature of 36°C having a collapse time of about or more than 60 seconds.

[0013] In one or more embodiments there is provided a substantially surfactant and polymeric agent free foamable composition comprising a short chain alcohol,

water, a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof or a synergistic combination of two or more fatty alcohols and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition; wherein the percent by weight is based on weight foamable composition; wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30. In one or more embodiments the ratio between a first fatty alcohol and a second fatty alcohol is between about 11:5 and about 5:11.

[0014] In one or more embodiments there is provided a method of preventing or ameliorating or eliminating or treating or alleviating a dermatological or mucosal disorder, comprising: applying a substantially surfactant and polymeric free foamable composition to a surface having a dermatological or mucosal disorder in need of treatment, said composition comprising a short chain alcohol, water, a foaming booster comprising at least one fatty alcohol or at least one fatty acid or combination thereof or a synergistic combination of two or more fatty alcohols and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition; wherein the percent by weight is based on weight foamable composition; wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and wherein upon dispensing the foamable carrier composition forms a foam that is thermally stable at a temperature of 36°C having a collapse time of about or more than 60 seconds.

[0015] Unexpectedly, it has been further discovered that quality hydro foamable formulations and foams, which are substantially free of SCA, can be achieved without the presence of significant amounts of standard surface active agents known in the art, by using the carrier discovered for hydro-alcoholic foams without the SCA. Also surprisingly they can form quality foamable formulations and foams even in the absence of customary polymeric agents. Thus, in one or more embodiments, there is provided a substantially surfactant free hydro foamable formulation or foam. In one or more preferred embodiments the hydro formulations and foams are free of surface active agents. Thus, in one or more embodiments, there is also provided a substantially polymeric agent free hydro foamable

formulation or foam. In one or more preferred embodiments the hydro formulations and foams are free of polymeric agents. Thus, in one or more embodiments, there is provided a substantially surfactant free and polymeric agent free hydro- foamable formulation or foam. Thus, in one or more other embodiments, there is provided a surfactant free and polymeric agent free hydro- foamable formulation or foam.

[0016] In one or more embodiments, the foamable formulation is clear or transparent when pressurized by the propellant. In a further embodiment the foamable formulation is clear or transparent prior to addition of one or more active agents at which point it forms a homogenous suspension of active agent. Yet, in certain other embodiments the formulation is a suspension prior to addition of propellant and remains a suspension when pressurized by the propellant.

[0017] According to an embodiment the one or more active agents is selected from the group consisting of an active herbal extract, an acaricides, an age spot and keratose removing agent, an allergen, an alpha hydroxyl acid, an analgesic agent, an anesthetic, an immunogenic substance, an antiacne agent, an antiallergic agent, an antiaging agent, an antibacterial agent, an antibiotic, an antiburn agent, an anticancer agent, an antidandruff agent, an antidepressant, an antidermatitis agent, an antiedemic anent, an antifungal agent, an antihistamine, an antihelminth agent, an antihyperkeratolyte agent, an anti-infective agent, an antiinflammatory agent, an antiirritant, an antilipemic agent, an antimicrobial agent, an antimycotic agent, an antioxidant, an antiparasitic agent, an anti-pigmentation agent, an antiproliferative agent, an antipruritic agent, an antipsoriatic agent, an antirosacea agent, an antiseborrheic agent, an antiseptic agent, an antiswelling agent, an antiviral agent, an anti-wart agent, an anti-wrinkle agent, an antiyeast agents, an astringent, a beta-hydroxy acid, benzoyl peroxide, benzoyl chloride a, topical cardiovascular agent, a chemotherapeutic agent, a corticosteroid, an immunogenic substance, a dicarboxylic acid, a disinfectant, a fungicide, a hair growth regulator, a haptene, a hormone, a hydroxy acid, an immunosuppressant, an immunoregulating agent, an immunomodulator, an insecticide, an insect repellent, a keratolytic agent, a lactam, a local anesthetic agent, a lubricating agent, a masking agent, a metals, a metal oxide, a mitocide, a neuropeptide, a non-steroidal anti-inflammatory agent, an oxidizing

agent, a pediculicide, a peptide, a protein, a photodynamic therapy agent, a radical scavenger, a refatting agent, a retinoid, a sanative, a scabicide, a self tanning agent, silicone talc, a skin protective agent, a skin whitening agent, a steroid, a steroid hormone, a steroidal antiinflammatory agent ,a vasoconstrictor, a vasodilator, a vitamin, a vitamin A, a vitamin A derivative, a vitamin B, a vitamin B derivative, a vitamin C, a vitamin C derivative, a vitamin D, a vitamin D derivative, a vitamin D analog, a vitamin F, a vitamin F derivative, a vitamin K, a vitamin K derivative, a wound healing agent and a wart remover and mixtures thereof. In a further embodiment the active agent is selected from the group consisting of mometasone furoate or betamethasone valerate, diclofenac sodium, and metronidazole

[0018] In an embodiment the composition comprises a fatty alcohol. The fatty alcohol can be a straight chain fatty alcohol, a saturated fatty alcohol, an unsaturated fatty alcohol, a hydroxyl substituted fatty alcohol or a branched fatty alcohol. In an embodiment the fatty alcohol is a therapeutically active fatty alcohol.

[0019] In additional embodiments, the foamable composition comprises a fatty acid. The fatty acid can be a straight chain fatty acid, a saturated fatty acid, an unsaturated fatty acid, a hydroxyl fatty acid or a branched fatty acid. In an embodiment the fatty acid is a therapeutically active fatty acid.

[0020] According to additional embodiments there is provided a method of producing a foamable composition, including:

1. providing a foamable therapeutic composition including a therapeutic agent at a therapeutically effective concentration, a short chain alcohol, for example, at a concentration of about 20% to about 60% by weight, a hydroalcoholic composition foaming booster (including at least a fatty alcohol or a fatty acid) and water
2. introducing the foamable composition in an aerosol packaging assembly, comprising a container, suitable for containing a pressurized product and a valve, capable of extruding a foam; and

3. introducing to the aerosol packaging assembly a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition.

[0021] In one or more certain embodiments the SCA content can be in excess of 60%, or in excess of 65%, however, as the level reaches towards 70% it is harder to prepare a satisfactory formulation and higher levels of hydro-alcoholic foam booster can be appropriate. In certain circumstances having both fatty acid and fatty alcohol may help. The greater challenge to form hydro-alcoholic foamable formulations and foam with very high levels of SCA's is presumably without being bound by any theory because of the defoaming and themolabile properties of the alcohol, the high level of alcohol and the lower level of water.

[0022] According to further embodiments there is provided a method of preventing, treating ameliorating or eliminating a disorder by selecting and releasing on to a convenient surface a safe and effective pharmaceutical or cosmetic foamable composition comprising an effective amount of a pharmaceutical or cosmetic agent, a short chain alcohol ("SCA"), water, a foaming booster and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition; directing the released foam on to a target on a patient in need; applying a shear force to and spreading the foam over the target surface such that after a simple rub the foam is no longer visible to the naked eye as it is absorbed rapidly on to the target surface.

[0023] According to one of more further embodiments the disorder treated by the foamable composition is selected from the group consisting of a dermatose, a dermatitis, a vaginal disorder, a vulvar disorder, an anal disorder, a disorder of a body cavity, an ear disorder, a disorder of the nose, a disorder of the respiratory system, a bacterial infection, a fungal infection, a viral infection, dermatosis, dermatitis, parasitic infections, disorders of hair follicles and sebaceous glands, scaling papular diseases, benign tumors, malignant tumors, reactions to sunlight, bullous diseases, pigmentation disorders, disorders of cornification, pressure sores, disorders of sweating, inflammatory reactions, xerosis, ichthyosis, an allergy, a burn,

a wound, a cut, a chlamydia infection, a gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, a yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, osteoarthritis, joint pain, an hormonal disorder, a pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, an anal and rectal disease, an anal abscess/fistula, anal cancer, an anal fissure, an anal wart, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum.

[0024] According to further embodiments there is provided the use of a foamable composition in the manufacture of a medicament for preventing or treating a dermatological or a mucosal disorder, the foamable composition comprising: a short chain alcohol; water; a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof; and a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition; wherein the foamable composition is substantially surfactant free; wherein the foamable composition is substantially polymeric agent free; wherein the percent by weight is based on weight foamable composition; wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and wherein upon dispensing the foamable composition forms a foam of quality that is thermally stable at a temperature of 36°C having a collapse time about or more than 60 seconds. In some embodiments, the foamable composition of the use further includes at least one active agent. In other embodiments, the foamable composition of the use comprises 0% to 0.4% surfactant and 0% to 0.2% polymeric agent.

DETAILED DESCRIPTION

Foamable composition and foam properties

[0025] The ability to achieve quality foam with a substantial concentration of at least one short chain alcohol without a surfactant is surprising, because such alcohols are not prone to creating a foam. The challenge is not just to achieve a quality foam but also to attain a formulation that will satisfy a plurality of two, three, four, five, six or more of the following property specifications simultaneously.

1. Uniformity: The composition should be formulated so that it is and can remain uniform without phase separation or precipitation over time. This property is of high importance when the product is intended to be a pharmaceutical product. In some embodiments the formulation is shaken before use and is readily re-homogenized upon shaking so the composition is uniform when dispensed.

2. Flowability: The composition, when placed in an aerosol container and pressurized should be flowable such that it can be expelled through the canister valve. It should preferably also be shakable inside the container. These requirements create a formulation challenge, because low or non-viscous flowable and shakable compositions are prone to undergo phase separation or precipitation.

3. Quality: Upon release from the can, the composition should generate a foam of good or excellent quality having low density and small bubble size.

4. Stability/Breakability: The fine balance between stability and breakability of the foam coming out of the container is very delicate: on one hand the foam should preferable not be “quick breaking”, i.e., it should be at least short term stable upon release from the pressurized container and not break as a result of exposure to skin temperature; and on the other hand, it should be “breakable”, i.e., it should spread easily, break down and absorb into the skin or membrane upon application of mild shear force.

5. Skin Feeling: To ensure patient compliance the skin feeling after application should be pleasant, and greasy or waxy residues should be minimal.

6. Non-irritating: The above requirements should be achieved with the awareness that formulation excipients, especially surfactants, can be irritating, and should preferably be eliminated from the composition or reduced as much as possible.

7. Delivery: Finally, the composition should also be designed to ensure efficient delivery of a therapeutic agent into the target site of treatment.

[0026] Based on extensive investigations and trial and error experiments, it has been found that such properties can be achieved for formulations as described below.

Compositions

[0027] All % values are provided on a weight (w/w) basis.

[0028] In one or more embodiments there is provided a foamable composition including:

1. a short chain alcohol
2. a foaming booster, at least one fatty alcohol, or at least one fatty acid, or a combination thereof or a synergistic combination of two or more fatty alcohols; and
3. water; and
4. a liquefied or compressed gas propellant.

[0029] In one or more other embodiments the fatty acid(s) and fatty alcohol(s) may combine to have a synergistic effect. In one or more further embodiments the fatty acid(s) and fatty acids(s) may combine to have a synergistic effect. In one or more embodiments the synergism is to improve foam quality. In one or more other embodiments the synergism is to improve foam thermal stability. In one or more other embodiments the synergism is to improve foam collapse time, which is can be an indicator of thermal stability.

[0030] In one or more embodiments the foamable composition is substantially surfactant free. In one or more other embodiments it is essentially surfactant free, namely a non surfactant composition.

[0031] In one or more embodiments the foaming booster combination is a synergistic combination that can improve the foam quality and or thermal stability of the composition.

[0032] In one or more embodiments the short chain alcohol, is preferably ethanol. In one or more embodiments the short chain alcohol, is preferably isopropanol. In one or more embodiments the short chain alcohol is at least about 15% by weight of the composition. In one or more embodiments the short chain alcohol is at a concentration of about 20% to about 60% by weight. In one or more embodiments the short chain alcohol is at a concentration of about 30% to about 60% by weight. In one or more embodiments the short chain alcohol is at a concentration of about 40% to about 60% by weight. In one or more other embodiments the SCA is propanol or butanol or a branched chain derivative thereof such as isopropanol or iso-butanol. In one or more embodiments it is a pentanol.

[0033] Upon release from an aerosol container, the foamable composition forms an expanded breakable foam suitable for topical administration. In one or more other embodiments the foam is a breakable foam that is thermally stable upon dispensing yet breaks easily upon application of shear force.

[0034] The foamable composition is suitable for administration to the to various body areas, including, but not limited to the skin, a body surface, a body cavity, a mucosal surface, e.g., the mucosa of the nose, mouth and eye, the ear, the respiratory system, the vagina or the rectum (severally and interchangeably termed herein "target site")

[0035] According to one or more embodiments, the foamable composition further comprises a cosmetic or a pharmaceutical active agent (severally and interchangeably termed herein "active agent").

[0036] In one or more embodiments there is provided a foamable composition including:

1. an active agent at an effective concentration;
2. a short chain alcohol, preferably ethanol, at a concentration of about 20% to about 60% by weight;
3. about 0.1% to about 10% by weight of at least one fatty alcohol, or at least one fatty acid, or a synergistic combination of two or more fatty alcohols,;
4. water; and
5. a liquefied or compressed gas propellant.

[0037] In one or more embodiments the composition is substantially polymeric agent free. In one or more embodiments the polymeric agent comprises less than about 0.2% by weight; less than about 0.1% by weight; or less than about 0.05% by weight of the formulation. In one or more embodiments the composition is essentially polymeric agent free comprising less than about 0.01% by weight of the formulation or having no polymer.

[0038] In one or more embodiments, at least a portion of the therapeutic agent is suspended or dissolved evenly throughout the entire composition.

[0039] In one or more embodiments, the foam composition is clear and transparent when placed under the pressure of the propellant. In one or more embodiments, the composition is transparent upon pressurization by the gas propellant.

[0040] It was found that formulations containing high amount of a SCA (such as ethanol) are not prone to foaming when using combinations of different types of surfactants and different types of polymers. Foams produced were not of quality and or collapsed rapidly. It was found that the combination of at least two suitable fatty alcohols (e.g stearyl alcohol with cetyl alcohol or cetyl alcohol with myristyl alcohol) or a combination of at least one fatty alcohol with at least one fatty acid (e.g stearyl alcohol with stearic acid) or the combination of at least two suitable fatty

acids (e.g myristic acid with stearic acid) produced good to excellent quality short term stable foams in the absence of customary surfactants and or in the absence of customary polymeric agents. It was further discovered that fatty alcohols or fatty acids with a saturated carbon chain of between 14 to 18 or between 16 to 18 carbons have outstanding foam boosting properties. Furthermore, the formulations of the present invention can provide foams of quality in the presence of various active ingredients.

[0041] Surprisingly, it was discovered that that the combination of at least two suitable fatty alcohols have synergistic foam boosting properties in the absence of customary surfactants and or in the absence of customary polymeric agents. For example when cetyl alcohol or myristyl alcohol were used alone in hydro-alcoholic formulations, poor and fairly good foams were obtained respectively. Surprisingly however, when myristyl alcohol was combined with cetyl alcohol at a 1:1 ratio, a short term stable breakable foam of excellent quality was obtained. Thus, the combination of cetyl and myristyl alcohol has a synergistic foam boosting effect.

[0042] It was further found that when cetyl alcohol or stearyl alcohol were used alone in hydro-alcoholic formulations, fairly good and good foams were achieved respectively. Surprisingly however, when stearyl alcohol was combined with cetyl alcohol at a 1:1 ratio, a short term stable breakable foam of excellent quality was obtained. Thus, the combination of cetyl and stearyl alcohol has a synergistic foam boosting effect.

[0043] Furthermore, when stearyl alcohol and stearic acid were used alone in hydro-alcoholic formulations, good quality foams were obtained. Surprisingly, breakable foam of excellent quality, having a low density was also obtained with a combination of stearic acid with stearyl alcohol at a 1:1 ratio.

[0044] Thus in one or more embodiments there is provided a hydro-alcoholic foamable formulation which provides an excellent breakable foam. In one or more embodiments the foam displays a collapse time of about 60 sec or more, or of about 90 seconds or more, or of about 120 seconds or more, or of about 150 seconds or

more, or of about 180 seconds or more at 36°C. In other words it displays a thermal stability on exposure to a body surface at normal body temperature.

[0045] In one or more embodiments the foam displays a collapse time of about 60 seconds or less, or of about 50 seconds or more, or of about 40 seconds or less, or of about 30 seconds or less at 36°C. In other words it displays a thermal liability on exposure to a body surface at normal body temperature.

[0046] In one or more embodiments the fatty acid or fatty alcohol has 14 to 18 carbon atoms in its carbon chain. In one or more embodiments the fatty acid or fatty alcohol has 16 to 18 carbon atoms in its carbon chain. In one or more embodiments the fatty acid or fatty alcohol has 18 carbon atoms in its carbon chain. In one or more other embodiments the fatty alcohol or fatty acid has 14 to 22 carbon atoms in its carbon chain. In one or more further embodiments the fatty alcohol or fatty acid has 16 to 22 carbon atoms in its carbon chain.

[0047] In one or more embodiments there is provided a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof. In one or more embodiments the combination is a synergistic combination. In certain embodiments the synergism results in an improved foam quality. In certain embodiments the synergism results in a thermal stability or in an improved thermal stability. In certain embodiments the thermal stability is exhibited when the composition is placed on a mammal at normal body temperature. In an embodiment the mammal is a human.

[0048] In one or more other embodiments the foaming booster consists essentially of at least one fatty alcohol or at least one fatty acid or a combination thereof. In one or more other embodiments the foaming booster consists essentially of at least two fatty alcohols. In one or more other embodiments the foaming booster consists essentially of at least two fatty acids. In one or more other embodiments the foaming booster is between about 1% and about 10% by weight of the composition.

[0049] In one or more embodiments the foamable formulation comprises a synergistic combination of two or more fatty alcohols to achieve a foam with thermal stability. In one or more embodiments, the foamable formulation comprises a synergistic combination of two or more fatty acids to achieve a foam with thermal stability. In one or more embodiments the foamable formulation comprises a synergistic combination of at least one fatty acid and at least one fatty alcohol to achieve a foam with thermal stability. In one or more embodiments, the foamable formulation comprises a synergistic combination of two or more fatty alcohols or fatty acids or a fatty acid and fatty alcohol at a ratio of about 1:1. By about it is intended to provide for a variation of 35% or of 30% or of 25% or of 20% or of 10% or of 5% or of 1% or any % between any of these amounts. If there are more than two fatty alcohols then in one or more embodiments the ratio between a first fatty alcohol (having the highest concentration) and the remaining fatty alcohols is between about 2:1 and about 1:2, or if there are more than two fatty acids then in one or more embodiments the ratio between the first fatty acid (having the highest concentration) and the remaining fatty acids is between about 2:1 and about 1:2, or if there is a combination of fatty acids and fatty alcohols and there are more than one of one or both of types in one or more embodiments the ratio between the total fatty alcohols and the total fatty acids is between about 2:1 and about 1:2. In one or more further embodiments the aforesaid ratios are between about 11:5 and about 5:11, or are in certain embodiments are about 1:1.

[0050] Surprisingly, foam quality and properties can be strongly influenced by the ratio of mixtures of two or more fatty alcohols, such as cetyl and stearyl alcohol or by the ratio of mixtures of two or more fatty acids, such as myristic acid and stearic acid or by the ratio of mixtures of at least one fatty alcohol and at least one fatty acid , such a stearyl alcohol and stearic acid.

[0051] Formulations having a cetyl:stearyl alcohol ratio of about 1:1 generated, for example, a breakable foam of quality being thermally stable on being applied to a surface at 36°C for at least 3 minutes. Whereas when the ratio of cetyl:stearyl alcohol was about more than 11:5 , or was about less than 5:11 no foam of quality was produced. Thus, in one or more embodiments, there is provided a hydro-

alcoholic foamable formulation of good quality being thermally stable on being applied to a surface at 36°C for at least a minute comprising about 1:1 cetyl:stearyl alcohol. In one or more embodiments it is thermally stable for at least two minutes. In one or more embodiments, it is thermally stable for at least three minutes. In one or more embodiments a quickly breaking foam of fairly good quality was produced when the ratio was about 5:11 cetyl:stearyl alcohol.

[0052] Interestingly, when surfactant was removed from prior art formulations (Example 1 of U.S. Patent No. 6,126,920) no foam was produced. Therefore, it appears that they rely on the surfactant present in combination with the alcohol in the composition to produce quick-breaking foams in complete contrast an teaching away from the surfactant-free hydro-alcoholic breakable foams, which are thermo stable at 36°C established herein.

[0053] In one or more other embodiments the fatty alcohol synergistic combination is cetyl and myristyl alcohol. In one or more other embodiments the fatty alcohol synergistic combination is stearyl and myristyl alcohol. In one or more other embodiments the fatty alcohol synergistic combination is stearyl and cetyl alcohol. In one or more embodiments, the ratio of fatty alcohols can be optimized in order to obtain foams of good or excellent quality. In an embodiment the ratio between at least two fatty alcohols is about 1:1. In an embodiment the ratio between at least of two fatty alcohols is about between 11:5 and 5:11. If there is more than two then in certain embodiments the ratio between the first (having the highest concentration) and the remaining fatty alcohols is between about 2:1 and about 1:2 or between about 11:5 and about 5:11 or about 1:1.

[0054] Surprisingly, it was found that foam of quality can be influenced by the ratio of combinations of at least two fatty acids (e.g myristic and stearic acid). Formulations having a myristic:stearic acid ratio of about 5:11 gave foams of good quality. In one or more embodiments, the ratio of fatty acids can be optimized in order to obtain foams of good or excellent quality.

[0055] Similarly, it has been found that foams containing cetostearyl alcohol in the composition have excellent quality and thermal stability at 36°C. It has further

been found that foams with higher amounts of cetostearyl alcohol have a lower density than foams containing lower amounts of cetostearyl alcohol. Thus, in one or more embodiments, there is provided a hydro-alcoholic foamable formulation or foam comprising between about 1% by weight and about 10% by weight of cetostearyl alcohol. In other embodiments the range of cetostearyl alcohol is between about 0.1% by weight and about 10% by weight ; about 1% by weight and about 15% by weight ; about 2% by weight and about 10% by weight ; about 3% by weight and about 10% by weight ; about 4% by weight and about 10% by weight ; about 5% by weight and about 10% by weight ; about 6% by weight and about 10%; about 7% by weight and about 10% by weight ; about 8% by weight and about 10% by weight ; about 5% by weight and about 12% by weight ; about 5% by weight and about 15% by weight ; about 0.1% by weight and about 15% by weight ; or about 0.1% by weight and about 5% by weight. In other embodiments the foam density is inversely correlated to the concentration of cetostearyl alcohol in the formulation within the range of about 1% by weight and about 7.5% by weight. The above ranges in one or more embodiments apply to the total % by weight of fatty acids, or to the total % by weight of fatty alcohols or to the total % by weight of fatty acids and fatty alcohols.

[0056] Surprisingly it has been found that foamable formulations containing different hydrocarbon propellants, produce breakable foams of good to excellent quality and having a low density and thermally stability yet breakable upon shear force. It was further found that the density is positively correlated with the concentration of the propellant i.e the lower the propellant the lower the foam density. It was further found that foams of good quality obtained in hydro-alcoholic formulations containing a hydrocarbon propellant at a concentration up to about 30%. These foams were thermally stable at 36°C for more than three minutes yet breakable upon shear force and had a low density. However, when the concentration of propellant was increased to about 37%, only poor quality foams were produced.

[0057] In one or more embodiments, there is provided a foamable formulation or breakable foam of good to excellent quality containing hydrocarbon propellant having a low density and being thermally stable for more than one, or two or three

minutes at 36°C yet breakable upon shear force. In one or more embodiments, there is provided a foam or a foamable formulation which comprises a hydrocarbon propellant selected from the group consisting of A-46 or Dymel 134a or AP-70. In one or more embodiments, there is provided a foam having a low density generated from a foamable formulation comprising at least one hydrocarbon propellant. In one or more embodiments, there is provided a foam having a density of less than about 0.2 g/ml; less than about 0.15 g/ml; less than about 0.1g/ml; less than about 0.09 g/ml; less than about 0.08 g/ml; less than about 0.07 g/ml; or less than about 0.06 g/ml generated from a foamable formulation comprising a hydrocarbon propellant. In one or more embodiments, hydro-alcoholic foams generated by hydrocarbon propellants at concentrations lower than 30% w/w have a density between about 0.06 g/ml and about 0.15 g/ml; or between about 0.03g/ml and about 0.2 g/ml. In one or more embodiments the density is positively correlated with the concentration of the propellant. In one or more embodiments the propellant concentration is within a range of about 6% by weight to about 14%; about 6% by weight to about 12%;about 6% by weight to about 10%; about 5% by weight to about 14%; about 6% by weight to about 16%; about 6% by weight to about 20%; about 6% by weight to about 30% by weight about 20% by weight to about 30%; about 20% by weight to about 35%; or about 30% by weight to about 35% by weight .

[0058] In one or more embodiments, there is provided a foamable formulation or breakable foam of good quality containing having a low density and being thermally stable for more than one, or two or three minutes at 36°C yet breakable upon shear force comprising isopropanol.

Short chain alcohol

[0059] A short chain alcohol according to one or more certain other embodiments, has up to 6 carbon atoms in their carbon chain skeleton and one hydroxy group. Such short chain alcohols can be selected from ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol, pentanol and isomers thereof (herein after “a pentanol) and hexanol and isomers thereof (herein after “a hexanol). In a preferred embodiment the short chain alcohol is ethanol. The SCA is present in a substantial amount. By a substantial amount is meant that the alcohol is present at a

% concentration by weight at which it is capable of having a defoaming effect and or an irritating effect. In various embodiments the amount of short chain alcohol is above about 10%. In one or more embodiments the alcohol is at least about15% by weight. In other embodiments it is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, or at least about 60% by weight. In one or more embodiments the SCA is at a concentration between about 15% to about 65% by weight, or about 20% to about 60% by weight, preferably between about 25% to about 55% by weight, and more preferably between about 30% to about 50% by weight.

Fatty alcohol

[0060] The hydro-alcoholic foamable composition foaming booster may include a fatty alcohol. The fatty alcohol which acts as a foam adjuvant is included in the foamable compositions as a main constituent, to evolve the foaming property of the composition and/or to stabilize the foam. In one or more embodiments , the fatty alcohol is selected from the group consisting of 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 myristyl alcohol (C14), arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). In one or more preferred embodiments , the fatty alcohol is cetyl alcohol, stearyl alcohol, behenyl alcohol or myristyl alcohol and combinations thereof.

[0061] Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are suitable as fatty alcohols in the context herein. In certain embodiments the amount of the fatty alcohol required to support the foam system can be approximately inversely related to the length of its carbon chains. Fatty alcohols are also useful in facilitating improved spreadability and absorption of the composition.

[0062] Fatty alcohols are amphiphatic, however unlike customary surfactants, they cannot usually function as stand-alone surfactants, because of their very weak

emulsifying capacity. They are occasionally used as non-ionic co-emulsifiers, i.e., and are commonly used as thickeners (*Surfactants in personal care products and decorative cosmetics*, by Linda D. Rhein, Mitchell Schlossman, Anthony O'Lenick, P., Third Edition, 2006, p. 247). Fatty alcohols are generally regarded as safe and they are not considered as irritants.

[0063] An important property of the fatty alcohols used in context of the composition disclosed herein is related to their therapeutic properties per se. Long chain saturated and mono unsaturated fatty alcohols, e.g., stearyl alcohol, erucyl alcohol, arachidyl alcohol and behenyl alcohol (docosanol) have been reported to possess antiviral, antiinfective, antiproliferative and anti-inflammatory properties (see, U.S. Patent No. 4,874,794). Longer chain fatty alcohols, e.g., tetracosanol, hexacosanol, heptacosanol, octacosanol, triacontanol, etc., are also known for their metabolism modifying properties and tissue energizing properties.

[0064] The concentration of a fatty alcohol or a combination of different fatty alcohols in the composition can in one or more embodiments range between about 0.1% and about 10%, or between about 1% to about 15%. In certain embodiments, the concentration of the fatty acid can be selected from the group consisting of (i) between about 0.1% and about 1%, (ii) between about 1% and about 5%, and (iii) between about 5% and about 10%. In one or more embodiments, the fatty alcohol is at a concentration at about 1% to about 3% by weight.

Fatty acid

[0065] The hydro-alcoholic foamable composition foaming booster may include a fatty acid or a combination of different fatty acids. In one or more embodiments the fatty acid can have 16 or more carbons in its carbon chain, such as myristic acid (C14), 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.

[0066] Optionally, the carbon atom chain of the fatty acid may have at least one double bond; alternatively, the fatty acid can be a branched fatty acid. The carbon chain of the fatty acid also can be substituted with a hydroxyl group, such as 12-

hydroxy stearic acid. In one or more preferred embodiments, the fatty acid is hexadecanoic acid, stearic acid or behenic acid or myristic acid , or combinations thereof.

[0067] The fatty acid or combination of fatty acids according to one or more embodiments can be included in the foamable composition in a concentration of 0.1% to 5%. In one or more embodiments the concentration of the combination of fatty acids in the composition can be selected from the group consisting of (i) between about 0.1% by weight and about 1%, (ii) between about 1% by weight and about 5%, and (iii) between about 5% by weight and about 10%. In one or more embodiments the a combination of myristylic acid and stearic acid is provided.

Fatty acid combined with Fatty alcohol

[0068] In one or more embodiments, the hydro-alcoholic foamable composition foaming booster may include a combination at least one fatty acid with at least one fatty alcohol to provide a thermally stable breakable foam. In one or more embodiments a thermally stable breakable foam of excellent quality is obtained by combining stearyl alcohol with stearic acid.

Propellant

[0069] The composition requires the addition of a propellant in order to generate a foam.

[0070] Suitable propellants include volatile hydrocarbons such as butane, propane, isobutene or mixtures thereof. In one or more embodiments a hydrocarbon mixture AP-70 is used. In one or more other embodiments a lower pressure hydrocarbon mixture AP-46 is used. Both contain butane, propane, isobutene although in different proportions. AP-46 is composed of about 16% w/w of propane, about 82% w/w of isobutane and about 2% w/w of propane. AP-70 is composed of about 50% w/w of propane, about 20% w/w of isobutane and about 30% w/w of propane. Hydrofluorocarbon (HFC) propellants are also suitable as propellants in the context disclosed herein. Exemplary HFC propellants include 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel

227). Dimethyl ether is also useful. In one or more embodiments use of compressed gases (e.g., air, carbon dioxide, nitrous oxide, and nitrogen) is also possible.

[0071] In one or more embodiments a combination of at least two propellants, selected from HFC, hydrocarbon propellants, dimethyl ether and compressed gases is contemplated.

[0072] Any concentration of the propellant, which affords an acceptable foam is useful in accordance with the present invention. In certain embodiments the propellant makes up between about 3% by weight and about 25% by weight of the foamable composition, or between about 20% by weight and about 30%, or between about 20% by weight and about 35% by weight and preferably between about 5% by weight and about 16% by weight of the composition.$ In preparing the formulations the ingredients other than propellant are combined to 100% and the propellant is added thereafter so that the ratio of formulation to propellant can range from 100:3 to 100:35, 100:3 to 100:30, 100:3 to 100:25 or preferably 100:5 to 100:16.

[0073] In one or more embodiments the propellant can also be used to expel formulation using a bag in can system or a can in can system as will be appreciated by someone skilled in the art. In certain embodiments the part of the propellant system is in the formulation and part separate from the formulation. In this way it is possible to reduce the amount of propellant in the formulation but still provide good expulsion from the canister, where the foamable formulation is expelled quickly but without jetting or noise. In one or more embodiments such system is used to expel foam into a body cavity where the amount of propellant released into the cavity is minimized.

[0074] Without being bound to any theory, it can be supposed that in certain embodiments in the absence of an independent oil phase, hydrocarbon propellant is partially solubilized by the SCA and the fatty alcohols and or fatty acids present in the composition, thus providing a clear composition. It was noted from a visual impaction that the fatty acids and alcohols were dissolved in the composition.

SUSPENSIONS

[0075] In one or more embodiments the active or cosmetic ingredient is completely soluble in the formulation or a phase thereof. In certain other embodiments it is provided as a suspension. For example, benzyl peroxide ('BPO') or microsponges comprising an active ingredient such as retinoic acid or other encapsulated bodies, such as described herein. The following description applied to BPO will also apply with the necessary changes to other solid agents, microspheres and other bodies. As can be appreciated, forming a homogeneous suspension of a BPO or other solid particle or body in foamable formulation using a formulation with high viscosity – so that even after addition of propellant the formulation has high viscosity - in order to try and stabilize the oil droplets and BPO particles, minimize particle motion and discourage gravitational sedimentation in the canister in which the formulation is stored simply will not do for foamable compositions. Such viscous formulations are not desirable for foamable compositions since they have low flowability and may exhibit one or more of the following: are not shakable; form a block, i.e., a solid with no flowable mass, in the canister; do not result in uniform expulsion; and if expulsed may be accompanied by unwanted phenomena such as one or more of jets, tailing and noise.

[0076] Unexpectedly it has been discovered that it is possible to make compositions which are truly flowable and have low viscosity in which the propellant forms part of the oil phase of the emulsion formulation but nevertheless surprisingly does not make the formulation substantially vulnerable to phase separation and or sedimentation. Moreover these compositions are stable and are able to form breakable foam of quality that spreads easily and is able to deliver an effective and measurable amount of active agent homogeneously to a target surface.

OPTIONAL INGREDIENTS

[0077] A further element and aid to reducing viscosity in the presence of small amounts of gelling agents is the use of a buffer or buffer complex, such as citrate buffer or alternatively lactate to cause a thick emulsion gel or paste containing carbomer to become fluid. Other similar buffers may work. Non limiting examples

of appropriate possible buffers, which may achieve the same objective are acetate, malate, sorbate, succinate and tartrate.

[0078] Optionally, the foamable composition further includes at least one organic carrier selected from the group consisting of a polar solvent, a hydrophobic organic carrier and mixtures thereof, at a concentration of about 2% to about 50% by weight.

Hydrophilic solvent

[0079] A hydrophilic solvent is a solvent that is more miscible with water than with a hydrophobic compound.

[0080] Examples of suitable hydrophilic solvents are , propylene glycol, low molecular weight polyethylene glycols, methoxyisopropanol, PPG-2 propyl ether, PPG-2 butyl ether, PPG-2 methyl ether, PPG-3 methyl ether, dipropylene glycol propyl ether, dipropylene glycol butyl ether, dipropylene glycol, methyl propanediol, propylene carbonate, water soluble/dispersible polypropylene glycols, ethoxylated polypropylene glycol, glycerin, sorbitol, hydrogenated starch hydrolysate, silicone glycols, and their mixtures and the like. In one or more embodiments water is a hydrophilic solvent.

[0081] In one or more embodiments, the composition comprises a hydrophilic solvent.

[0082] In one or more embodiments, the short chain alcohol is replaced by a hydrophilic solvent.

[0083] In one or more embodiments, the hydrophilic solvent is a polyol. A polyol is an organic substance that contains at least two hydroxy groups in its molecular structure. In one or more embodiments, the foamable carrier contains at least one diol. In one or more embodiments, the foamable carrier contains at least one triol. In one or more embodiments, the polyol is a mixture of polyols. In one or more embodiments, the mixture of polyols contains at least one diol and at least one triol. In one or more embodiments the hydrophilic solvent is a polar solvent.

[0084] In one or more embodiments, the hydrophilic solvent is selected from the group consisting of propylene glycol, low molecular weight polyethylene glycols and glycerin.

Polar solvent

[0085] A "polar solvent" is an organic solvent which is typically soluble in both water and oil.

[0086] In one or more embodiments, the polar solvent is a polyol. Polyols are organic substances that contain at least two hydroxy groups in their molecular structure.

[0087] In one or more embodiments, the polar solvent contains an diol (a compound that contains two hydroxy groups in its molecular structure), such as propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butanediol (e.g., 1,4-butaneediol), butanediol (e.g., 1,3-butaneediol and 1,4-butenediol), butynediol, pentanediol (e.g., 1,5-pentanediol), hexanediol (e.g., 1,6-hexanediol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

[0088] In one or more embodiments, the polar solvent contains a triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin and 1,2,6-Hexanetriol.

[0089] Additional examples of polar solvents include polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, alkanols, such as dialkylamino acetates, and admixtures thereof, dimethyl isosorbide, ethyl proxitol, dimethylacetamide (DMAc) and alpha hydroxy acids, such as lactic acid and glycolic acid.

[0090] According to still other embodiments, the polar solvent is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including

PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof.

[0091] Yet, in additional embodiments, the polar solvent is an aprotic polar solvents, such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile, acetone, methyl ethyl ketone, 1,4-Dioxane and tetrahydrofuran (THF). Additional non-limiting examples include N-methylpyrrolidone, pyridine, piperidine, dimethyl ether, hexamethylphosphorotriamide, dimethylformanide, methyl dodecyl sulfoxide, N-methyl-2-pyrrolidone and 1-methyl-2-pyrrolidinone) and azone (1-dodecylazacycloheptan-2-one).

[0092] Many polar solvents, for example propylene glycol, glycerin, DMSO and azone possess the beneficial property of a dermal, transdermal or trans-mucosal drug delivery enhancer.

[0093] In one or more embodiments, the polar solvent is a dermal, transdermal or trans-mucosal drug delivery enhancer.

[0094] Many polar solvents, for example propylene glycol and glycerin, possess the beneficial property of a humectant.

[0095] In one or more embodiments, the polar solvent is a humectant.

Hydrophobic solvent/Emollient

[0096] One or more hydrophobic solvents are optionally included in the composition, in order to add to the sensory properties of the composition and/or in order to impart skin conditioning properties. In an embodiment, the hydrophobic solvent is an emollient, i.e., a substance that softens and soothes the skin. Emollients are used to correct dryness and scaling of the skin. The hydrophobic solvent and/or the emollient can be selected from the group consisting of mineral oil, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, 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, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, maleated soybean oil, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer. In certain embodiments the carrier can comprise a petrolatum where it is provided in modest or minor amounts of up to about 5%.

[0097] In one or more preferred embodiments the hydrophobic solvent has at least a degree of solubility in the SCA present in the formulation.

[0098] In order to improve the miscibility or the dispersion of a hydrophobic solvent in the formulation, fatty alcohols and preferably fatty acids can be added in order to form an emulsion which is either stable or easily re-dispersible by shaking. In certain embodiments small amounts of polymeric agents may be added up to about 0.2%. By re-dispersible on shaking is meant that the formulation on reasonable moderate shaking of about a few times will provide a uniform emulsion which will remain relatively stable for at least a reasonable short period of time sufficient to allow it to be dispensed from the pressurized canister. In one or more embodiments a combination of one or more fatty acids with one or more fatty alcohols is used to help provide an emulsion which has at least a short term stability and is easily redispersable on shaking.

Modulating Agent

[0099] In one or more embodiments the formulation includes a modulating agent. The term modulating agent is used to describe an agent which can improve the stability of or stabilize a foamable carrier or composition and or an active agent

by modulating the effect of a substance or residue present in the carrier or composition.

[0100] In one or more embodiments the substance or residue may for example be acidic, basic or a buffer agent, which can affect pH in a composition. The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound. In certain embodiments the modulating agent is a buffer, as defined by Van Slyke [Van Slyke, J. Biol. Chem. 52, 525 (1922)], as "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH."

[0101] Certain active agents are known to be stable at a narrow pH range. For example, corticosteroids are typically stable at acidic pH levels, while vitamin D3 derivatives are stable at basic pH. Hence, in certain embodiments the modulating agent is selected to exert a pH modifying effect, which results in the desirable pH level.

[0102] In certain embodiments, the pH modifying agent is selected from the group including citric acid and sodium citrate.

[0103] It is important to maintain skin surface pH in order to prevent susceptibility to bacterial skin infections or skin damage and disease. Thus, adding a modulating agent, which contributes to the stabilization of skin pH at the desirable level, is advantageous.

[0104] In the same fashion, adding an acidic modulating agent to a foamable composition, which is intended for vaginal application is advantageous, since better protection against vaginal infection is attained with pH lower than about 4.5.

[0105] In an embodiment, the modulating agent is an antioxidant or a radical scavenger. Non-limiting examples of antioxidants/radical scavengers are ascorbic acid and derivatives, tocopherol or derivatives thereof (succinate, or sorbate or

acetate or other esters), propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Non-limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non-limiting examples of negative ionization agents are sodium lauryl sulfate, sodium lauryl lactylate and phospholipids.

[0106] In one or more further embodiments the modulating agent is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the solvent to enable it to "mop up" or "lock" metal ions. In one or more embodiments a preferred non limiting example is EDTA.

[0107] Modulating agents may be added to the compositions of the subject invention, as necessary to provide their function of improving the stability of or stabilize a foamable carrier or composition and or an active agent. The modulating agent concentration can preferably range from about 0.1% to about 10%, more preferably from about 1% to about 5%, of the composition. In certain cases the active agent itself is the modulating agent, alone or in combination with another modulating agent, and in such cases it will be added at an effective dose which may be outside these ranges. For example azelaic acid may be at about 15% by weight of the composition.

Additional components

[0108] In an embodiment, a composition disclosed herein includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, bulking agents, cleansers, colorants, skin conditioners, deodorants, diluents, dyes, fragrances, hair conditioners, herbal extracts, humectants, keratolytic agents, pearlescent aids, perfuming agents, pH preservatives, protectants, skin penetration or permeation enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers, flavanoids and vitamins. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

[0109] In one or more further embodiments the composition further includes about 0.1% to about 5% of a humectant. In one or more further embodiments the

humectant is selected from the group consisting of PEG 400, propylene glycol and glycerin or mixtures of two or more thereof.

SUBSTANTIALLY SURFACTANT FREE

[0110] According to one or more embodiments, the foamable composition is substantially surfactant-free. In the context herein, the term "substantially surfactant free composition" relates to a composition that contains a total of less than about 0.2% of a surfactant selected from the group consisting of non-ionic, anionic, cationic, zwitterionic, amphoteric and ampholytic surfactants. Preferably, the composition comprises less than about 0.2% by weight by weight of a surfactant and more preferably less than about 0.1%. Non-surfactant compositions will comprise no or negligible levels of surface active agents (essentially surfactant free). In some embodiments, the foamable composition contains between about 0% and 0.2% surfactant, or between about 0% and 0.1% surfactant.

[0111] In the art, the term surface active agent or surfactant is sometimes used loosely and some publications may refer to compounds that have a supportive role, such as co-surfactants as surfactants. Substances which cannot function as true surfactants on their own but only in the context of being used with a surfactant are not considered to be surfactants for the purposes described herein. Thus, in the context herein, a fatty alcohol is not regarded a surfactant, and likewise, a fatty acid is not regarded as a surfactant In contrast, however, an ether or an ester formed from them can be a surfactant. Also quaternary ammonium compounds and ions, which for example are not infrequently seen in hair preparations, are not regarded as surfactants.

SUBSTANTIALLY POLYMER FREE

[0112] According to one or more embodiments, the foamable composition is substantially polymeric agent free. In the context herein, the term "substantially polymeric agent free composition" relates to a composition that contains a total of less than about 0.2% by weight of a polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent, being locust bean gum, sodium alginate, sodium caseinate, egg

albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers, semi-synthetic polymeric materials such as cellulose ethers, such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, and cationic celluloses, carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene); poloxamers (synthetic block copolymer of ethylene oxide and propylene) ; polyethylene glycol having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) and which could function as a hydro alcoholic foam booster. Preferably, the composition comprises less than about 0.1% by weight by weight of a polymeric agent and more preferably less than about 0.05%. Non-polymeric agent compositions i.e. essentially polymeric agent free compositions will comprise no or negligible levels of polymeric agents. According to one or more embodiments, the foamable composition is essentially polymeric agent free. In some embodiments, the foamable composition contains between 0% and 0.2% polymeric agent, between 0% and 0.1% polymeric agent, or between 0% and 0.05% polymeric agent. In some embodiments, the foamable composition contains between 0.05% and 0.2% polymeric agent, or between 0.05% and 0.1% polymeric agent, or between 0.1% and 0.2% polymeric agent.

[0113] In the art, the term polymeric agent can be used loosely to refer to any polymer. However, polymers that do not have a hydro-alcoholic foam boosting role but may act in other ways, for example polyethylene glycols, such as PEG 400, which are liquid hydrophilic polymeric solvents, are not excluded from the

compositions. Similarly a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer and the like, which can provide a good feeling to the composition are not excluded. Also particles made of polymeric substance, such as is microcapsules, microspheres, nanocapsules, nanospheres, polymer matrix, silica-gel, and microsponges are not excluded from the compositions. Further polymeric active agents are not excluded from the composition.

PHYSICAL CHARACTERISTICS OF THE FOAMABLE COMPOSITION AND FOAM

[0114] A foamable composition manufactured according to one or more embodiments herein is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0115] In one or more embodiments the foamable composition is a single phase solution. In certain circumstances, where the active agent is insoluble and is presented as a homogenous suspension and the formulation is turbid or cloudy. In one or more other embodiments the formulation prior to addition of propellant is an emulsion. In one or more embodiments the foam composition has an acceptable shelf-life of at least one year, or at least two years at ambient temperature. A feature of a product for cosmetic or medical use is long term stability. Propellants, which are a mixture of low molecular weight hydrocarbons, tend to impair the stability. The foamable compositions herein are surprisingly stable, even in the absence of customary surfactants. Surprisingly they also form stable breakable foams even in the absence of customary polymeric agents.

[0116] 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.

[0117] The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam. Compositions containing a substantial amount of semi-solid hydrophobic solvents, e.g., white petrolatum, as the main ingredients of the oil phase of the emulsion, will likely exhibit high viscosity and poor flowability and are inappropriate candidates for a foamable composition.

Foam Quality

[0118] Foam quality can be graded as follows:

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

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

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

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

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

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

[0119] Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge

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

Foam Density

[0120] Another property of the foam is specific gravity or density, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.20 g/mL or less than 0.12 g/mL, depending on their composition and on the propellant concentration.

Shakability

[0121] 'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. Shakability is described further in the section on Tests. In one or more certain limited embodiments the formulation is poorly shakable but is nevertheless flowable.

Breakability / collapse time

[0122] A further aspect of the foam is breakability. The balance between stability and breakability of the foam coming out of the container is very delicate: on one hand the foam should preferably not be "quick breaking", i.e., it should be stable upon release from the pressurized container and not break as a result of exposure to skin temperature; and on the other hand, it should be "breakable", i.e., it should spread easily, break down and absorb into the skin or membrane upon application of mild shear force. The breakable foam is thermally stable, yet breaks under shear force. Sheer-force breakability of the foam is clearly advantageous over thermally-induced breakability. Thermally sensitive foams start to collapse immediately upon exposure to skin temperature and, therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

[0123] The collapse time of foam represents its tendency to be temperature-sensitive and its ability to be at least short term stable so as to allow a user sufficient time to comfortably handle and apply the foam to a target area without being rushed and or concerned that it may rapidly collapse, liquefy and or disappear. Collapse

time, as an indicator of thermal sensitivity, is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C.

[0124] Short chain alcohols are known to cause foam to be thermolabile and "quick breaking". However, in certain embodiments herein, despite the presence of high alcohol content, quite unexpectedly the foam is substantially thermally stable. By "substantially thermally stable" it is meant that the foam upon application onto a warm skin or body surface at about 35-37°C does not collapse within about 30 seconds. Thus, in one or more embodiments the simple collapse time of the foam is more than about 30 seconds or more than about one minute or more than about two minutes. In one or more limited embodiments simple collapse time can be a little shorter than 30 seconds, but not less than about 20 seconds. In one or further or alternative embodiments the collapse time is measured by introducing a sample of foam into an incubator at 36 °C and the collapse time of the foam is more than 30 seconds or more than about one minute or more than about two minutes.

PHARMACEUTICAL COMPOSITION

[0125] The foamable composition is an ideal vehicle for active pharmaceutical ingredients and active cosmetic ingredients. In the context active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents". In one or more embodiments the active agent is soluble in the composition of a phase thereof. In one or more other embodiments it is insoluble. When insoluble the active agent is presented as a suspension or on a carrier which can include microspheres and the like.

[0126] Suitable active agents include but are not limited to an active herbal extract, an acaricides, an age spot and keratose removing agent, an allergen, an alpha hydroxyl acid, an analgesic agent, an antiacne agent, an antiallergic agent, an antiaging agent, an antibacterial agent, an antibiotic, an antiburn agent, an anticancer agent, an antidandruff agent, an antidepressant, an antidermatitis agent, an antiedemic anent, an antifungal agent, an antihistamine, an antihelminth agent, an antihyperkeratolyte agent, an anti-infective agent, an antiinflammatory agent, an

antiirritant, an antilipemic agent, an antimicrobial agent, an antimycotic agent, an antioxidant, an antiparasitic agent, an antiproliferative agent, an antipruritic agent, an antipsoriatic agent, an antirosacea agent, an antiseborrheic agent, an antiseptic agent, an antiswelling agent, an antiviral agent, an anti-wart agent, an anti-wrinkle agent, an antiyeast agents, an astringent, a beta-hydroxy acid, benzoyl peroxide, a topical cardiovascular agent, a chemotherapeutic agent, a corticosteroid, an immunogenic substance, a dicarboxylic acid, a disinfectant, a fungicide, a hair growth regulator, a haptene, a hormone, a hydroxy acid, an immunosuppressant, an immunoregulating agent, an immunomodulator, an insecticide, an insect repellent, a keratolytic agent, a lactam, a local anesthetic agent, a lubricating agent, a masking agent, a metal, a metal oxide, a mitocide, a neuropeptide, a non-steroidal anti-inflammatory agent, an oxidizing agent, a pediculicide, a peptide, a protein, a photodynamic therapy agent, a radical scavenger, a refatting agent, a retinoid, a sanative, a scabicide, a self tanning agent, a skin protective agent, a skin whitening agent, a steroid, a steroid hormone, a vasoconstrictor, a vasodilator ,a vitamin, a vitamin A, a vitamin A derivative, a vitamin B, a vitamin B derivative, a vitamin C, a vitamin C derivative, a vitamin D, a vitamin D derivative, a vitamin D analog, a vitamin F, a vitamin F derivative, a vitamin K, a vitamin K derivative, a wound healing agent and a wart remover. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

Encapsulation of an active agent

[0127] In one or more embodiments, the active agent is encapsulated in particles, microparticles, nanoparticles, microcapsules, microspheres, nanocapsules, nanospheres, liposomes, niosomes, polymer matrix, silica-gel, graphite, nanocrystals or microsponges. Such particles can have various functions, such as (1) protection of the drug from degradation; (2) modification of the drug release rate from the composition; (3) control of skin penetration profile; and (4) mitigation of adverse effects, due to the controlled release of the active agent from the encapsulation particles.

Solubility of an active agent

[0128] In an embodiment , the active agent is not fully soluble in water or, is not fully soluble in the SCA, is not fully soluble in the presence of a hydrophobic solvent in the formulation, or is not fully soluble in the oil phase of the emulsion. In one or more embodiments the active agent is soluble in the composition or a phase thereof. In an embodiment, the aprotic polar solvent is present in the composition in an amount sufficient to solubilize the active agent in the composition. In one or more embodiments, aprotic polar solvent acts to improve the solubility of an active agent. In certain preferred embodiments, the active agent to be solubilized is selected from the group consisting of a non-steroidal anti-inflammatory agent, a local anesthetic agent, a steroid, an immunomodulators, a keratolytically active agent, an anti-acne agent, an anti-rosacea agent, an antiinfective agent and an anti-psoriasis agent. In a preferred embodiment the active agent to be solubilized is diclofenac.

Exemplary groups of active agents

Steroids

[0129] In an embodiment, the active agent is a steroid. In certain embodiments the steroid is a corticosteroid, including but not limited to, bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone valerate and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone,

hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, as well as analogs, derivatives, salts, ions and complexes thereof.

[0130] In certain embodiments, the steroid is a hormone or a vitamin, as exemplified by pregnane, cholestane, ergostane, aldosterone, androsterone, calcidiol, calciol, calcitriol, calcipotriol, clomegestone, cholesterol, corticosterone, cortisol, cortisone, dihydrotestosterone, ergosterol, estradiol, estriol, estrone, ethinylestradiol, fusidic acid, glucocorticoid, lanosterol, mometasone furoate, prednisolone, prednisone, progesterone, spironolactone, timobesone and testosterone, as well as analogs, derivatives, salts, ions and complexes thereof.

[0131] In an embodiment, the aprotic polar solvent is present in the composition in an amount sufficient to solubilize the steroid.

NSAID

[0132] In an embodiment, the active agent is a non-steroidal anti-inflammatory agent. In the context a nonsteroidal antiinflammatory agent (also termed herein "NSAID") is a pharmaceutically active compound, other than a corticosteroid, which affects the immune system in a fashion that results in a reduction, inhibition, prevention, amelioration or prevention of an inflammatory process and/or the symptoms of inflammation and or the production pro-inflammatory cytokines and other pro-inflammatory mediators, thereby treating or preventing a disease that involves inflammation.

[0133] In one or more embodiments, the NSAID is an inhibitor of the cyclooxygenase (COX) enzyme. Two forms of cyclooxygenase are known today: the constitutive cyclooxygenase (COX-1); and the inducible cyclooxygenase (COX-2), which is pro-inflammatory. Thus, in one or more embodiments , the NSAID is selected from the group consisting of a COX-1 inhibitor, a COX-2 inhibitor or a non-selective NSAID, which simultaneously inhibits both COX-1 and COX-2.

[0134] In one or more embodiments, the NSAID is salicylic acid a salicylic acid derivatives. Exemplary salicylic acid derivative include, in a non limiting fashion, aspirin, sodium salicylate, choline magnesium trislicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, olsalazine, esters of salicylic acid with a carboxylic acid, esters of salicylic acid with a dicarboxylic acid, esters of salicylic acid with a fatty acid, esters of salicylic acid with a hydroxyl fatty acid, esters of salicylic acid with an essential fatty acid, esters of salicylic acid with a polycarboxylic acid, and any compound wherein salicylic acid is linked to an organic moiety through a covalent bond.

[0135] In one or more embodiments, the NSAID is para-aminophenol (e.g., acetaminophen) and salts and derivatives thereof.

[0136] In one or more embodiments, the NSAID is an indole or an indole - acetic acid derivative (e.g., indomethacin, sulindac, etodolac) and salts and derivatives thereof.

[0137] In one or more embodiments, the NSAID is an aryl acetic acids (e.g., tolmetin, diclofenac, ketorolac) and salts and derivatives thereof.

[0138] In one or more embodiments, the NSAID is an arylpropionic acid and salts and derivatives thereof. Exemplary arylpropionic acid derivative include, in a non limiting fashion, are ibuprofen, naproxen, flubiprofen, ketoprofen, fenoprofen, oxaprozin.

[0139] In one or more embodiments, the NSAID is anthranilic acids or an anthranilic acid derivative, also termed "fenamates" (e.g., mefenamic acid, meclofenamic acid) and salts and derivatives thereof.

[0140] In one or more embodiments, the NSAID is selected from the group of enolic acids, enolic acid salts, enolic acid esters, amides, anhydrides and salts and derivatives thereof. Non-limiting examples of enolic acid derivatives include oxicams (piroxicam, tenoxicam) and pyrazolidinediones (phenylbutazone, oxyphenthratrazone)

[0141] Yet, in additional embodiments, the NSAID is an alkanone (e.g., nabumetone).

[0142] Selective COX-2 Inhibitors include, in an exemplary manner diaryl-substituted furanones (e.g., Rofecoxib); diaryl-substituted pyrazoles (e.g., Celecoxib); indole acetic acids (e.g., Etodolac); and sulfonanilides (e.g., Nimesulide) and salts and derivatives thereof.

[0143] In an embodiment, the aprotic polar solvent is present in the composition in an amount sufficient to solubilize the NSAID, as exemplified herein by the solubilization of diclofenac.

Local anesthetic agents

[0144] In an embodiment, the active agent is a local anesthetic agent. Without limiting the scope , the anesthetic agent can be selected from the group consisting of benzocaine, lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine, phenol, any pharmaceutically acceptable salts thereof and mixtures of such anesthetic agents. Any mixture of synergistically beneficial anesthetic agents is contemplated. In an embodiment, the aprotic polar solvent is present in the composition in an amount sufficient to solubilize the anesthetic agent.

Keratolytically active agents

[0145] A keratolytic agent may be included as an active agent of a foamable composition. The term "keratolytically active agent" as used herein includes a compound that loosens and removes the stratum corneum of the skin, or alters the structure of the keratin layers of skin. Keratolytically active agents are used in the treatment of dermatological disorders that involve dry skin, hyperkeratinization (such as psoriasis), skin itching (such as xerosis), acne and rosacea.

[0146] 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. Dihydroxybenzene and derivatives thereof have been recognized as potent keratolytic agents. Resorcinol (m-dihydroxybenzene) and derivatives thereof are used in anti-acne preparations. In addition to hydroquinone (p-dihydroxybenzene) having anti-pigmentation properties, hydroquinone is also known to be keratolytic. These compounds also exhibit antiseptic properties. Cresols also possess bactericidal and keratolytic properties.

[0147] Vitamin A and vitamin A derivatives, also termed herein "retinoids", such as retinoic acid, isoretinoic acid, retinol and retinal, as well as adapalene, tazarotene, isotretinoin, acitretin and additional retinoids known in the art of pharmaceuticals and cosmetics are another class of keratolytically active agents.

[0148] 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.

[0149] Another class of keratolytically active agents includes urea and urea derivatives.

Immunomodulators

[0150] In an embodiment, the active agent is an immunomodulator. Immunomodulators are chemically or biologically-derived agents that modify the immune response or the functioning of the immune system. Immunomodulators suitable for use according to the present invention include, among other options, cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod, as well as analogs, derivatives, salts, ions and complexes thereof. Such compounds, delivered in the foam, are especially advantageous in skin disorders such as psoriasis, eczema and atopic dermatitis, where the large skin areas are to be treated. In an embodiment, the aprotic polar solvent is present in the composition in an amount sufficient to solubilize the immunomodulator.

Retinoids

[0151] In an embodiment, the active agent is a retinoid. Retinoids suitable for use according to the present invention include, among other options, retinol, retinal, retinoic acid, isotretinoin, tazarotene, adapalene, 13-cis-retinoic acid, acitretin all-trans beta carotene, alpha carotene, lycopene, 9-cis-beta-carotene, lutein and zeaxanthin, as well as any additional retinoids known in the art of pharmaceuticals and cosmetics; and analogs, derivatives, salts, ions and complexes thereof.

Anti-acne and anti-rosacea active agents

[0152] In an embodiment, the active agent is an anti-acne or an anti-rosacea agent. The anti-acne agent can be selected from the group consisting of resorcinol, sulfur, salicylic acid and salicylates, alpha-hydroxy acids, nonsteroidal anti-inflammatory agents, benzoyl peroxide, retinoic acid, isoretinoic acid and other retinoid compounds, adapalene, tazarotene, azelaic acid and azelaic acid derivatives, antibiotic agents, such as erythromycin and clyndamycin, coal tar, zinc salts and complexes, and combinations thereof, in a therapeutically effective concentration.

Antipsoriasis agents

[0153] In an embodiment, the active agent is an anti-psoriasis agent. Such anti-psoriasis agent can be selected, among other options, from the group of keratolytically-active agents, salicylic acid, coal tar, anthralin, corticosteroids, vitamin D and derivatives and analogs thereof, including vitamin D3 analogs such as calcitriol, calcipotriol; retinoids, and photodymamic therapy agents.

Antiinfective agents

[0154] In an embodiment, the active agent is an anti-infective agent. Such anti-infective agent can be selected from the group of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent. Exemplary antiinfective agents are exemplified by beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, metronidazole, an antibiotic glycopeptide, a macrolide, erythromycin, clindamycin,

an antibiotic nucleoside, an antibiotic peptide, polymyxin B, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, fucidic acid, mupirocin, chloramphenicol, a sulfonamide, tetracycline, an antibiotic metal, silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium, an oxidizing agent, iodine, iodate, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, chlorohexidine, a triguanide, a bisbiguanide, a polymeric biguanide and a naturally occurring antibiotic compound, as well as analogs, derivatives, salts, ions and complexes thereof.

The foamable composition essential ingredients as active agents

[0155] In certain embodiments, the short chain alcohol possesses therapeutic properties on its own and therefore, it can be regarded as "active agent". For example, ethanol kills microorganisms and can be effective in the treatment or prevention of conditions that involve microbial infection, such as bacterial, fungal and viral conditions. Additionally, the defatting effect of alcohol is useful for the treatment of conditions which involve oily skin, such as acne, Rosacea and seborrheic dermatitis. The combination of a short chain alcohol and a therapeutically effective fatty alcohol or fatty acid may afford a synergistic beneficial effect in conditions characterized, for example, by infection and/or inflammation.

[0156] Because short chain alcohols are known to increase the rate of absorption of some compounds through organic tissues including skin and nails, formulations comprising such alcohols can be used as a drug delivery system.

Combination of active agents

[0157] Several disorders involve a combination of more than one etiological factor; and therefore, the use of more that one active agents is advantageous. For example, psoriasis involves excessive cell proliferation and inadequate cell differentiation as well as inflammation. Atopic dermatitis involves keratinocyte growth abnormality, skin dryness and inflammation. Bacterial, fungal and viral

infections involve pathogen colonization at the affected site and inflammation. Hence, in many cases, the inclusion of a combination of active agents in the foamable pharmaceutical composition can be desirable. Thus, in one or more embodiments, the foamable composition further includes at least two active agents, in a therapeutically effective concentration.

Fields of Applications

[0158] The foamable composition is suitable for treating any inflicted surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a mucosal surface and a body cavity, e.g., the cavity and/or the mucosa of the nose, mouth and eye, the ear, the respiratory system, the vagina or the rectum (severally and interchangeably termed herein "target site"). The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating a dermatological or a mucosal disorder.

[0159] By selecting a suitable active agent, or a combination of two or more active agents, the foamable composition is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell

carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing moistens, gangrene, scarring, and vitiligo. The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating any of the preceding disorders.

[0160] Likewise, the foamable composition is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum. The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating any of the preceding disorders.

[0161] In an embodiment the composition is useful for the treatment of an infection. In one or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection. The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating any of the preceding disorders.

[0162] In an embodiment the composition is useful for the treatment of wound, ulcer and burn. The foamable composition is suitable for use in the manufacture of a medicament for treating wounds, ulcers, and burns.

[0163] In an embodiment the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

[0164] The composition is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone. The foamable composition is suitable for use in the manufacture of a medicament to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

[0165] In an embodiment the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

[0166] In an embodiment the disorder is selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, granuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria,

hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo, chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; and wherein the active agent is suitable for treating said disorder. The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating any of the preceding disorders

[0167] In one embodiment the disorder is an inflammation, skin inflammation, acne, rosacea, actinic keratosis, skin cancer, a local pain, joint pain and ostheoarthritis; the active agent is a nonsteroidal anti-inflammatory drug, given at a therapeutically effective concentration. The foamable composition is suitable for use in the manufacture of a medicament for preventing or treating any of the preceding disorders. The foamable composition is suitable for use in the manufacture of a medicament including any of the preceding active agents.

[0168] In one or more embodiments, the active agent may be a placebo or a cosmetic agent. The foamable composition is suitable for use in the manufacture of a medicament including a placebo or active agent.

Cosmetic use

[0169] In one or more embodiments, the composition may be used for cosmetic use. For example it may be used as part of a cosmetic formulation to prevent a cosmetic disorder or to improve the skin. Alternatively it may be used with cosmetic effect for example as a cosmetic remover. It can be dispensed in small quantities as a foam targeted to a surface and applied locally with mechanical force causing the foam to break.

EXAMPLES

[0170] The invention is described with reference to the following examples, in a non-limiting manner. The following examples exemplify the foamable compositions and methods described herein. The examples are for the purposes of illustration only and are not intended to be limiting. Many variations will suggest themselves and are within the full intended scope.

Example 1 - General Manufacturing Procedures

[0171] The following procedures are used to produce the foam samples described in the examples below, in which only the steps relevant to each formulation are performed depending on the type and nature of ingredients used.

[0172] **Step 1:** Ethanol and, if present, humectants are mixed at room temperature. Polymers or gelling agents, if present, are added at room temperature under mixing until formulation homogeneity is obtained. Surfactants and fatty alcohols or fatty acids, if present, are added under agitation until complete dissolution.

[0173] **Step 2:** Any pH-buffering agents are added to water at room temperature under mixing until complete dissolution.

[0174] **Step 3:** The alcoholic phase is added to the water phase under mixing until homogeneity is obtained.

[0175] **Step 4:** The formulation is packaged in aerosol canisters which are crimped with a valve, pressurized with propellant and equipped with an actuator

suitable for foam dispensing. Optionally a metered dosage unit can be utilized to achieve delivery of repeatable measured doses of foam, for example as described in U.S. Provisional Application No. 61/363,577 entitled "APPARATUS AND METHOD FOR RELEASING A UNIT DOSE OF CONTENT FROM A CONTAINER," filed July 12, 2010, which is incorporated herein by reference.

[0176] Note: hydrophobic substances, if present, are added to the alcohol phase with the fatty alcohols and or fatty alcohols.

Materials

Table 1 - Exemplary possible ingredients suitable for the production of foamable compositions disclosed herein. Equivalent materials from other manufacturers can also be used satisfactorily.

Chemical Name	**Function**	**Commercial Name**	**Supplier**
Acrylates/C10-30 alkyl acrylate crosspolymer	Gelling agent	Pemulen TR2	Noveon
Behenyl alcohol	Foam adjuvant	Lanette 22	Cognis
Benzoyl Peroxide	Active agent	Benzoyl Peroxide	Spectrum
Betamethasone Valerate	Active agent	Betamethasone Valerate	Crystal Pharma
Carbomer 934P	Gelling agent	Carbopol 934P	Spectrum
Cetostearyl alcohol	Foam adjuvant	Speziol C16-C18	Cognis
Cetyl alcohol	Foam adjuvant	Speziol C16	Cognis
Citric acid	pH modifying agent	Citric acid	R. de Haen
Clindamycin Phosphate	Active agent	Clindamycin Phosphate	Uqifa
Coco-betaine	Surfactant	Dehyton	Cognis
Diclofenac sodium	Active agent	Diclofenac sodium	Sriken
Ethanol absolute	Solvent	Ethanol	Bio Lab

Glycerin	Humectant	Glycerin	Cognis
Hexylene Glycol	Solvent	Hexylene Glycol	Spectrum
Hydroxypropyl cellulose	Gelling agent	Klucel EF	Hercules
Hydroxypropyl methylcellulose	Gelling agent	Methocel K100M	Colorcon Dow
Laureth-23	Surfactant	Brij 35P	Uniqema
Myristic acid	Foam adjuvant	Myristic acid	Spectrum
Myristyl alcohol	Foam adjuvant	Speziol C14	Cognis
Oleth-20	Surfactant	Samulsol 98	Seppic
PEG-40 Stearate	Surfactant	Myrj 52S	Croda
Poloxamer 407	Gelling agent	Lutrol F127	BASF
Polyethylene glycol 400	Humectant	PEG-400	Inoes
Polysorbate 60	Surfactant	Polysorbate 60	Cognis
Propane/Isobutane/Butane (16:82:2)	Propellant	A-46	Aeropress Corporation
Propane/Isobutane/Butane (55:18:27)	Propellant	AP-70	Aeropress Corporation
Propylene glycol	Humectant	Propylene Glycol	Gadot
Sodium citrate	pH modifying agent	Sodium Citrate	Archer Daniels Mild
Sodium lauryl sarcosinate	Surfactant	Lanette E PH	Cognis
Sodium Lauryl Sulfate	Surfactant	Sodium dodecyl sulfate	Cognis
Stearic acid	Foam adjuvant	Stearic acid	Spectrum
Stearyl Alcohol	Foam adjuvant	Speziol C18	Cognis
Tetrafluoroethane	Propellant	Dymel 134a	DuPont
Triethanolamine	pH modifying agent	TEA	Gadot
Xanthan Gum	Gelling agent	Xanthan Gum 11K	CP Kelco US

Production under vacuum

[0177] Optionally, the foamable carrier may be produced under nitrogen and under vacuum. Whilst the whole process can be carried out under an oxygen free environment, it can be sufficient to apply a vacuum after heating and mixing all the ingredients to obtain an emulsion or homogenous liquid. Preferably the production chamber is equipped to apply a vacuum but if not the formulation can be for example placed in a desiccator to remove oxygen prior to filing and crimping.

Canisters Filling and Crimping

[0178] Each aerosol canister is filled with the pre-foam formulation ("PFF", i.e., foamable carrier) and crimped with valve using vacuum crimping machine. The process of applying a vacuum will cause most of the oxygen present to be eliminated. Addition of hydrocarbon propellant may without being bound by any theory further help to reduce the likelihood of any remaining oxygen reacting with the active ingredient. It may do so, without being bound by any theory, by one or more of dissolving in, to the extent present, the oil or hydrophobic phase of the formulation, by dissolving to a very limited extent in the aqueous phase, by competing with some oxygen from the formulation, by diluting out any oxygen, by a tendency of oxygen to occupy the dead space, and or by oxygen occupying part of the space created by the vacuum being the unfilled volume of the canister or that remaining oxygen is rendered substantially ineffective in the formulation.

Pressurizing & Propellant Filling

[0179] Pressurizing is carried out using a hydrocarbon gas or gas mixture. Canisters are filled and then warmed for 30 seconds in a warm bath at 50°C and well shaken immediately thereafter.

TESTS

[0180] By way of non-limiting example the objectives of hardness, collapse time and freeze-thaw cycle ("FTC") stability tests are briefly set out below as would be appreciated by a person of the art.

Collapse Time

[0181] Collapse Time, which is the measure of thermal stability, is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. The collapse time result is defined as the time when the foam height reaches 50% of its initial height or if the foam has not yet reached 50% of its initial height after say 180 seconds then the collapse time is recorded as being >180. By way of illustration one foam may remain at 100% of its initial height for three minutes, a second foam may reach 90% of its initial height after three minutes, a third foam may reach 70% of its initial height after three minutes, and a fourth foam may reach 51% of its initial height after three minutes, nevertheless in each of these four cases the collapse time is recorded as >180secs since for practical purposes for easy application by a patient to a target the majority of the foam remains intact for more than 180secs. If the foam for example reaches 50% of its original height after say 100 seconds it would be recorded as having a collapse time of 100 seconds. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 minute. Foams which are structurally stable on the skin for at least one minute are termed "short term stable" carriers or foams.

[0182] Alternatively, a Simple Collapse Time can be assessed by placing a foam sample on the warm fingers of a volunteer and measuring the time it takes to melt on the fingers, for example, as observed in Example 4 herein.

Density

[0183] In this procedure, the foam product is dispensed into vessels (including dishes or tubes) of a known volume and weight. Replicate measurements of the mass of foam filling the vessels are made and the density is calculated. The canister and contents are allowed to reach room temperature. Shake the canister to mix the contents and dispense and discard 5-10 mL. Then dispense foam into a pre-weighed tube, filling it until excess is extruded. Immediately remove (level off) excess foam at both ends and weigh the filled tube on the weighing balance.

Viscosity

[0184] Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1RPM may be measured, although the figures are of a higher magnitude. Unless otherwise stated viscosity of the pre-foam formulation (PFF) is provided. It is not practical to try and measure the viscosity of the foamable formulation with regular propellants since they have to be stored in sealed pressurized canisters or bottles. In order to simulate the viscosity in the foamable formulations with propellant an equivalent weight of pentane (a low volatile hydrocarbon) is added to and mixed with the pre-foam formulation and left overnight. The viscosity is then measured as above.

FTC (Freeze Thaw Cycles)

[0185] Foam appearance under extreme conditions of repeated heating and cooling is evaluated by cycling through cooling, heating, (first cycle) cooling, heating (second cycle) etc., conditions, commencing with -10°C (24 hours) followed by +40°C (24 hours) and measuring the appearance following each cycle. The cycle is repeated for up to three times.

Chemical Stability

[0186] The amount of active agent present is analyzed in foam expelled from various pressurized canisters containing foam formulations using HPLC. Analysis is carried out at zero time and at appropriate time intervals thereafter. The canisters are stored in controlled temperature incubators at one or more of 5C, at 25C, at, 40C and at 50C. At appropriate time intervals canisters are removed and the amount of active agent in the foam sample is measured.

Bubble Size

[0187] Foams are made of gas bubbles entrapped in liquid. The bubble size and distribution reflects in the visual texture and smoothness of the foam. Foam bubbles size is determined by dispensing a foam sample on a glass slide, taking a picture of the foam surface with a digital camera equipped with a macro lens. The diameter of

about 30 bubbles is measured manually relatively to calibration standard template. Statistical parameters such as mean bubble diameter, standard deviation and quartiles are then determined. Measuring diameter may also be undertaken with image analysis software. The camera used is a Nikon D40X Camera (resolution 10MP) equipped with Sigma Macro Lens (ref: APO MACRO 150mm F2.8 EX DG HSM). Pictures obtained are cropped to keep a squared region of 400 pixels x 400 pixels.

Microscope size:

[0188] The light microscope enables observing and measuring particles from few millimeters down to one micron. Light microscope is limited by the visible light wavelength and therefore is useful to measuring size of particles above 800 nanometers and practically from 1 micron (1,000 nanometers).

Shakability

[0189] Shakability represents the degree to which the user is able to feel / hear the presence of the liquid contents when the filled pressurized canister is shaken. Shaking is with normal mild force without vigorous shaking or excessive force. When the user cannot sense the motion of the contents during shaking the product may be considered to be non-shakable. This property may be of particular importance in cases where shaking is required for affecting proper dispersion of the contents.

Shakability scoring:

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

Example 2 – Hydro-alcoholic formulations containing a combination of surfactants and polymers

[0190] Several surfactants were used in combination with gelling agents (polymers) and checked for their foaming properties.

[0191] As described in Table 2a below, formulations 1, 7, 8 and 12 containing laureth-23 or oleth-20 non-ionic surfactants in combination with various polymers did not give rise to foams but merely generated bubbly liquids.

Table 2a: Formulations containing laureth-23 or oleth-20

Formulation	**1**	**7**	**8**	**12**
Ingredient	**% w/w**	**% w/w**	**% w/w**	**% w/w**
Ethanol	51.00	51.50	50.50	51.00
Purified water	36.00	40.00	40.90	36.90
PEG 400	–	–	5.00	5.00
Propylene glycol	5.00	–	–	–
Glycerin	–	5.00	–	–
Hydroxypropyl cellulose	–	–	1.50	–
Poloxamer 407 20% solution	5.00	–	–	5.00
Carbomer 974	–	0.40	–	–
Triethanolamine	–	0.10	–	–
Laureth-23	2.00	2.00	2.00	–
Oleth-20	–	–	–	2.00
Citric acid	0.40	0.40	0.07	0.07
Sodium citrate	0.60	0.60	0.03	0.03
Total	100.00	100.00	100.00	100.00
Propellant AP-70	8.00	8.00	8.00	8.00
Results				
Foam Quality	Poor	Poor	Poor	Poor
Product Clarity	Yes	No	Yes	Yes

[0192] As described in Table 2b below, formulations 2, 5 and 11 containing polysorbate 60 and PEG 40 stearate non-ionic surfactants in combination with various polymers did not give rise to foams but merely generated bubbly liquids.

Table 2b: Formulations containing polysorbate 60 and PEG 40 stearate

Formulation	**2**	**5**	**11**
Ingredient	**% w/w**	**% w/w**	**% w/w**
Ethanol	50.50	51.50	51.50
Purified water	40.00	40.00	40.90
PEG400	–	–	5.00
Propylene glycol	–	5.00	–
Glycerin	5.00	–	–
Hydroxypropyl cellulose	1.50	–	–
Hydroxypropyl methylcellulose	–	0.50	–
Carbomer 974	–	–	0.40
Triethanolamine	–	–	0.10
Polysorbate 60	0.60	0.60	0.60
PEG 40 Stearate	1.40	1.40	1.40
Citric acid	0.40	0.40	0.07
Sodium citrate	0.60	0.60	0.03
Total	100.00	100.00	100.00
Propellant AP-70	8.00	8.00	8.00
Results			
Foam Quality	Poor	Poor	Poor
Product Clarity	Yes	Yes	No

[0193] As described in Table 2c below, formulations 3, 9 and 10 containing sodium lauryl sulfate and coco-betaine (anionic and zwitterionic surfactants) in combination with various polymers did not give rise to foams but merely generated bubbly liquids.

Table 2c: Formulations containing sodium lauryl sulfate and coco-betaine

Formulation	**3**	**9**	**10**
Ingredient	**% w/w**	**% w/w**	**% w/w**
Ethanol	52.90	52.40	51.90
Purified water	40.00	36.90	40.90
PEG 400	5.00	–	–
Propylene glycol	–	–	5.00
Glycerin	–	5.00	–
Hydroxypropyl cellulose	–	–	1.50
Poloxamer 407 20% solution	–	5.00	–
Hydroxypropyl methylcellulose	0.50	–	–
Sodium lauryl sulfate	0.30	0.30	0.30
Coco-betaine	0.30	0.30	0.30
Citric acid	0.40	0.07	0.07
Sodium citrate	0.60	0.03	0.03
Total	100.00	100.00	100.00
Propellant AP-70	8.00	8.00	8.00
Results			
Foam Quality	Poor	Poor	Poor
Product Clarity	Yes	Yes	Yes

[0194] As described in Table 2d below, formulations 17 and 18 containing sodium lauryl sarcosinate and sodium cetearyl sulfate anionic surfactants in combination with various polymers did not give rise to foams but merely generated bubbly liquids.

Table 2d: Formulations containing sodium lauryl sarcosinate and sodium cetearyl sulfate

Formulation	**017**	**018**
Ingredient	**% w/w**	**% w/w**
Ethanol	52.90	52.40
Purified water	40.90	36.90
PEG 400	5.00	–
Glycerin	–	5.00
Poloxamer 407 20% solution	–	5.00
Hydroxypropyl methylcellulose	0.50	–
Sodium lauryl sarcosinate	0.30	0.30
Sodium cetearyl sulfate	0.30	0.30
Citric acid	0.07	0.07
Sodium citrate	0.03	0.03
Total PFF components:	100.00	100.00
Propellant AP-70	8.00	8.00
Results		
Foam Quality	Poor	Poor
Product Clarity	Yes	Yes

[0195] As described in Table 2e below, formulations 52, 53 and 54 containing polymeric agents alone such as Hydroxypropyl cellulose (a cellulose-based polymer), poloxamer 188 (a polymer having some surfactant-like properties) and Acrylates/C10-30 alkyl acrylate crosspolymer (an amphiphilic polymer said to have some emulsifying-like properties) did not give foams but bubbly liquids.

Table 2e: Formulations containing various polymeric agents

Formulation	**52**	**53**	**54**
Ingredient	**% w/w**	**% w/w**	**% w/w**
Ethanol	50.00	50.00	50.00
Purified water	47.00	47.00	47.00
Hydroxypropyl cellulose	3.00	–	1.50
Poloxamer 188	–	3.00	–
Acrylates/C10-30 alkyl acrylate crosspolymer	–	–	3.00
Total	100.00	100.00	100.00
Propellant AP-70	8.00	8.00	8.00
Results			
Foam Quality	Poor	Poor	Poor

[0196] This study shows that polymeric agents alone or combinations of polymeric agents one of which has some surfactant like properties are not sufficient to achieve good foaming properties in case of water-based vehicles containing large amounts of short chain alcohols.

[0197] Surfactant alone, polymer alone, surfactant plus polymer and combinations of polymers, one of which has surfactant like properties all failed to produce a quality hydro-alcoholic foam. This is a surprising result considering that based on the prior art, surfactants are known as useful foam boasting agents, especially when used in combination with polymeric agents. It appears that high levels of SCA's e.g. ethanol have an apparent defoaming effect or destabilizing effect, and thus it is not at all obvious how to obtain good quality foams with high levels of short chain alcohols.

Example 3 - Hydro-alcoholic formulations containing fatty alcohols and/or fatty acids

[0198] The influence of fatty alcohols and fatty acids on the foaming properties of hydro-alcoholic formulations was studied.

[0199] As described in Table 3 below, good quality foams can be obtained with fatty alcohol. Likewise, good quality foams can be achieved with certain fatty acids.

For example formulation 40 containing stearic acid gave a good quality foam, whereas formulation 41 containing isostearic acid only resulted in a bubbly liquid. Without being bound by any theory isostearic acid, which is non linear and liquid in contrast to stearic acid being linear and solid and may generate some steric hindrance and lower viscosity. Thus, the present invention is not limited to fatty alcohols and fatty alcohol combinations but includes also the use of fatty acids and fatty acid combinations as stabilizing agents in hydro-alcoholic foams alone or in combination with fatty alcohols (see e.g. example 9). All the formulations were surprisingly successful in the absence of a customary surfactant and in the absence of a customary polymeric agent

[0200] To evaluate the possible importance of the carbon chain length on the foaming properties of hydro-alcoholic formulations, several fatty alcohols containing from 14 to 22 carbons were used to create foams. Surprisingly, fatty alcohols comprising 14 carbons (myristyl alcohol) or 22 carbons (behenyl alcohol) on their own only produced bubbly liquids as shown in formulations 42 and 45. However, fatty alcohol having a carbon chain length of 16 to 18 gave foams of fairly good to excellent quality. For example, cetyl alcohol (C16) provided fairly good quality foam and stearyl alcohol gave good quality foams, as shown in formulations 43 and 44. Very surprisingly, the combination of cetyl alcohol and stearyl alcohol is synergistic and results in excellent quality foams as shown in formulation 46 which contains cetostearyl alcohol, a mixture of 50% cetyl alcohol and 50% stearyl alcohol. Such excellent quality foam was not observed in the examples containing either cetyl alcohol alone or stearyl alcohol alone. Thus, we have discovered that a combination of two fatty alcohols having a carbons chain length of 16 to 18 has a synergistic effect and substantially enhances the foaming properties of hydro-alcoholic formulations.

Table 3: Formulations containing fatty alcohols and fatty acids of different carbon chain length

Formulation	**40**	**41**	**42**	**43**	**44**	**45**	**46**
Ingredient	**%w/w**	**%w/w**	**%w/w**	**%w/w**	**%w/w**	**%w/w**	**%w/w**
Ethanol	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Water	47.00	47.00	47.00	47.00	47.00	47.00	47.00
Stearic acid (C18)	3.00	-	-	-	-	-	-
Isostearic acid (C18)	-	3.00	-	-	-	-	-
Myristyl alcohol (C14)	-	-	3.00	-	-	-	-
Cetyl alcohol (C16)	-	-	-	3.00	-	-	-
Stearyl alcohol (C18)	-	-	-	-	3.00	-	-
Behenyl alcohol (C22)	-	-	-	-	-	3.00	-
Cetostearyl alcohol (C16 + C18)	-	-	-	-	-	-	3.00
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Propellant AP-70	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Results							
Foam Quality	Good	Poor	Poor	Fairly Good	Good	Fair	Excel-lent

Example 4 – Thermal stability - comparative example

[0201] A foam formulation (Formulation 46B) was compared with a foam formulation from patent US 6,126,920, Example 1, as described in Table 4. Both foam samples were placed on fingers of a male volunteer and the thermal stability of each of the foams was assessed by measuring the time it takes to melt on the fingers. The foam formulation 46B was thermally stable and did not melt on contact with the skin for more than three minutes, thus providing an easy and convenient application for the user of the product. In contrast, the foam formulation from US patent 6,126,920, Example 1, which is described as a "quick-breaking" foam, was thermally unstable and quickly liquefied and melted on contact with the skin within

15 seconds, making the product application difficult for the user and causing the drug to absorb on the fingers, rather than on the intended target site of treatment.

Table 4: Comparative example

Formulation	**46B**	**Sample according to US 6,126,920 Example 1**
Ingredient	**% w/w**	**% w/w**
Ethanol	50.00	57.79
Purified water	47.00	33.69
Propylene glycol	–	2.00
Cetostearyl alcohol	3.00	–
Citric acid	–	0.073
Potassium citrate	–	0.027
Polysorbate 60	–	0.40
Octadecan-1-ol (stearyl alcohol)	–	0.50
Cetyl alcohol	–	1.10
Betamethasone valerate	0.12	0.12
Total	**100**	
Hydrocarbon propellant (butane/propane/isobutane)	8.00	4.30
Total		**100**
Results		
Time to 50% melting	**> 3 minutes**	**15 seconds**

Example 5 - Hydro-alcoholic formulations examining the effect of replacing cetostearyl alcohol with polymer

[0202] Parameters such as foam quality, collapse time and product clarity were evaluated, and results described in Table 5 below. The presence of a fatty alcohol (or similarly a fatty acid) seems compulsory, given that the formulation lacking cetostearyl alcohol did not give foam but a bubbly liquid.

Table 5: Formulations with and without cetostearyl alcohol

Formulation	**29**	**30**
Ingredient	**% w/w**	**% w/w**
Ethanol	50.20	50.20
Purified water	43.20	43.00
Propylene glycol	5.00	5.00
Hydroxypropyl cellulose	1.50	-
Cetostearyl alcohol	–	1.70
Citric acid	0.07	0.07
Sodium citrate	0.03	0.03
Total	100.00	100.00
Propellant AP-70	8.00	8.00
Results		
Foam Quality	Poor	Excellent
Collapse Time at 36°C (sec)	-	>180
Product clarity	Yes	Yes

Example 6 - Hydro-alcoholic formulations containing different concentrations of fatty alcohol

[0203] Parameters such as foam quality, collapse time and foam density were evaluated in foam formulations containing various concentrations of fatty alcohol, and the results are described in Table 6 below. Breakable foams of excellent quality were obtained in hydro-alcoholic formulations containing from 1% to 10% Cetostearyl alcohol. Interestingly, it appears that foams containing high amounts of cetostearyl alcohol have a lower density than foams containing lower amounts of cetostearyl alcohol. In one or more embodiments there is provided a low density foam. In some embodiments the density is about 0.1 g/mL or less. In some embodiments the density is about 0.08 g/mL or less. In some embodiments the density is about 0.07 g/mL or less. In some embodiments the density is about 0.06 g/mL.

Table 6: Formulations containing different concentrations of fatty alcohol

Formulation	**55**	**56**	**57**	**58**	**59**	**60**	**61**
Ingredient	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**
Ethanol	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Purified water	40.0	40.0	40.0	40.0	40.0	40.0	40.0
Propylene glycol	9.0	8.0	7.0	6.0	5.0	2.5	-
Cetostearyl alcohol	1.0	2.0	3.0	4.0	5.0	7.5	10.0
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
AP-70	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Results							
Foam Quality	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Collapse Time	>180	>180	>180	>180	>180	>180	>180
Foam Density	0.114	0.073	0.084	0.060	0.065	0.060	0.060

Example 7 - Hydro-alcoholic formulations containing different propellant types and amounts

[0204] Parameters such as foam quality, collapse time and foam density were evaluated in foam formulations containing different propellant types and amounts as described in Table 7a below. Breakable foams of excellent quality were obtained in hydro-alcoholic formulations containing A-46, Dymel 134a and various amounts of AP-70. Interestingly, it appears that foams containing hydrocarbon propellants have a low density as well as foams containing low amounts of propellant. Surprisingly, it was observed that as the amount of propellant increased form 6% to 8% to 12% to 14% the density also increased in small amounts. Further, examination of the results of Example 7b show that this phenomena continues as the propellant is increased to 20% and 30%. So by varying the amount of propellant and type the density of resultant foam can be modified. In some embodiments the density is about 0.2 g/mL or less. In some embodiments the density is about 0.16 g/mL or less. In some embodiments the density is about 0.12 g/mL or less. In some embodiments the density is about 0.11 g/mL or less.

Table 7a: Formulations containing different concentrations of fatty alcohol

Formulation	**62**	**63**	**64**	**65**	**66**	**67**
Ingredient	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**
Ethanol	50.0	50.0	50.0	50.0	50.0	50.0
Purified water	40.0	40.0	40.0	40.0	40.0	40.0
Propylene glycol	7.0	7.0	7.0	7.0	7.0	7.0
Cetostearyl alcohol	3.0	3.0	3.0	3.0	3.0	3.0
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
AP-70	6.00	10.00	12.00	14.00	-	-
A-46	-	-	-	-	8.00	-
Dymel 134a	-	-	-	-	-	8.00
Results						
Foam Quality	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Collapse Time	>180	>180	>180	>180	>180	>180
Foam Density	0.068	0.073	0.082	0.090	0.063	0.093

[0205] As can be seen from the experiment below there is a limit as to how much propellant can be added. Breakable foams of good quality were obtained in hydro-alcoholic formulations containing AP-70 at a concentration up to about 30%. These foams were thermally stable at 36°C for more than 3 minutes yet breakable upon shear force. However, with propellant amounts of about 37%, only poor quality foams were produced. Without being bound by any theory this may in part be connected to the hydro-alcoholic nature of the formulations and high ethanol level.

Table 7b: Formulations containing different concentrations of propellant

Formulation	**68**	**69**	**70**
Ingredient	**% w/w**	**% w/w**	**% w/w**
Ethanol	50.0	50.0	50.0
Purified water	40.0	40.0	40.0
Propylene glycol	7.0	7.0	7.0
Cetostearyl alcohol	3.0	3.0	3.0
Total	**100.00**	**100.00**	**100.00**
AP-70	20.00	30.00	37.00
Results			
Foam Quality	Good	Good	Poor
Collapse Time	>180	>180	-
Foam Density	0.121	0.158	-

Example 8 - Hydro-alcoholic formulations containing different ratios of fatty alcohol

[0206] Parameters such as foam quality, collapse time and foam density were evaluated in foam formulations containing different ratios of cetyl alcohol and stearyl alcohol as described in Table 8 below.

Table 8: Formulations containing different ratios of fatty alcohol

Formulation	**71**	**72**	**73**	**74**	**75**
Ingredient	**% w/w**	**% w/w**	**% w/w**	**% w/w**	**% w/w**
Ethanol	58.0	58.0	58.0	58.0	58.0
Purified water	32.0	32.0	32.0	32.0	32.0
Propylene glycol	8.4	8.4	8.4	8.4	8.4
Cetyl alcohol	1.5	1.1	0.8	0.5	0.1
Stearyl alcohol	0.1	0.5	0.8	1.1	1.5
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
AP-70	8.00	8.00	8.00	8.00	8.00
Results					
Foam Quality	Poor	Fair	Good	Fairly Good	Fair
Collapse Time	-	-	>180	Rapid	-
Foam Density	-	-	0.144	-	-
Cetyl:stearyl alcohol ratio	15:1	2.2:1 (i.e.11:5)	1:1	1:2.2 (i.e.5:11)	1:15

[0207] Surprisingly, it appears that the foam quality can be strongly influence by the ratio of mixtures of fatty alcohols such as cetyl and stearyl alcohol. Formulations having a cetyl:stearyl alcohol ratio of about 1 gave breakable quality foam being stable for more than 3 minutes at 36°C. However, when the ratio of cetyl:stearyl alcohol was about 11:5 or higher, or was about 1: 15 or lower, no quality foam could be produced. It was further noted that stearyl alcohol appears to have a more significant role in the synergistic relationship than cetyl alcohol. In contrast, it appears that Example 1 of U.S. Patent No. 6,126,920 relies on the surfactant present in the composition to produce quick-breaking foams. In short the prior art did not contemplate surfactant-free and polymer–free hydro-alcoholic that can produce thermally stable breakable foams.

Example 9 - Hydro-alcoholic formulations containing fatty alcohol and fatty acids

[0208] Parameters such as foam quality, collapse time and foam density were evaluated in foam formulations containing mixtures of fatty alcohol and fatty acids as described in Table 9 below.

Table 9a: Formulations mixtures of fatty alcohol and fatty acids

Formulation	**76**	**77**
Ingredient	**% w/w**	**% w/w**
Ethanol	58.0	58.0
Purified water	32.0	32.0
Propylene glycol	8.4	8.4
Cetyl alcohol	0.8	-
Myristyl alcohol	0.8	-
Stearyl alcohol	-	0.8
Stearic acid	-	0.8
Total	**100.00**	**100.00**
AP-70	8.00	8.00
Results		
Foam Quality	Excellent	Excellent
Collapse Time at 36°C (sec)	85	>180
Foam Density (g/mL)	0.093	0.074

[0209] When cetyl alcohol and myristyl alcohol are used alone in hydro-alcoholic formulations, poor and fairly good foams are obtained respectively, as shown in formulations 42 and 43 described in Example 3. Poor foam collapses rapidly. Surprisingly however, when 0.8% myristyl alcohol is combined with 0.8% cetyl alcohol, a short term stable breakable foam of excellent quality is achieved having a low density and a collapse time well in excess of a minute. So the combination of cetyl alcohol and myristyl alcohol achieves a synergistic effect. When stearyl alcohol and stearic acid are used alone in hydro-alcoholic formulations, good quality foams are obtained, as shown in formulations 40 and 44

described in previous example 3. Surprisingly however, a breakable foam of excellent quality having a low density and with a collapse time in excess of 180 sec at 36°C was obtained with a combination of 0.8% stearic acid with 0.8% stearyl alcohol.

[0210] In one or more embodiments, there is provided a hydro-alcoholic foamable formulation which provides a short term stable breakable foam with a collapse time of 60 sec or more at 36°C, and containing a combination of two or more fatty alcohols. In one or more embodiments the combination is synergistic.

[0211] In one or more embodiments, there is provided a hydro-alcoholic foamable formulation which provides a short term stable breakable foam with a collapse time of 180 seconds or more at 36°C, and containing a combination of one or more fatty alcohols with one or more fatty acids.

Example 10 - Hydro-alcoholic formulations containing different ratios of fatty acid

[0212] Parameters such as foam quality, collapse time and foam density were evaluated in foam formulations containing different ratios of myristic acid and stearic acid as described in Table 10 below.

Table 10: Formulations containing different ratios of fatty acid

Formulation	**79**	**80**	**81**
Ingredient	**% w/w**	**% w/w**	**% w/w**
Ethanol	58.0	58.0	58.0
Purified water	32.0	32.0	32.0
Propylene glycol	8.4	8.4	8.4
Myristic acid	1.1	0.8	0.5
Stearic acid	0.5	0.8	1.1
Total	**100.00**	**100.00**	**100.00**
AP-70	8.00	8.00	8.00
Results			
Foam Quality	Poor	Fairly Good	Good
Myristic:stearic acid ratio	2.2:1 (i.e.11:5)	1:1	1:2.2 (i.e.5:11)

[0213] Surprisingly, it appears that the foam quality can be influenced by the ratio of mixtures of fatty acids, such as myristic and stearic acid. Formulations having a myristic:stearic acid ratio between about 5:11 gave foams of good quality. However, when the ratio of myristic:stearic acid was about 11:5 only poor quality could be produced. In one or more embodiments, the ratio of fatty acids can be optimized in order to obtain foams of good or excellent quality. In one or more embodiments the combination of two or more fatty acids can enable lower amounts to be used. So whilst stearic acid alone can produce good quality foam at higher concentrations (see Example 3) as can be seen herein lower amounts were used in combination with myristic acid

Example 11 - Hydro-alcoholic formulations containing isopropanol

[0214] A foam formulation was prepared containing isopropanol (C_3H_7OH), which is another example of short chain alcohol. Parameters such as foam quality and collapse time were evaluated. As described in Table 11, a foam of good quality that did not collapse after 180 seconds was obtained in a formulation containing isopropanol.

Table 11: Formulation containing isopropanol

Formulation	**82**
Ingredient	**% w/w**
Isopropyl alcohol	40.00
Hexylene Glycol	12.00
Purified Water	31.00
Propylene Glycol	13.00
Stearyl alcohol	4.00
Total	**100.00**
Propellant AP70	8.00
Results	
Foam Quality	Good
Foam Density (g/mL)	0.223
Collapse Time at 36°C (sec)	>180

[0215] So, it follows that the above revelations as to how to achieve a short term stable breakable foam that is a foam which is stable upon exposure to body temperature despite the presence of a high level of ethanol should apply likewise mutatis mutandis to other short chain alcohols, such as, isopropanol, propanol, butanaol, iso-butanol, t-butanol and pentanol. In one or more embodiments there is provided a short term stable breakable foam formulation comprising one or more short chain alcohols.

AMENDED CLAIMS
received by the International Bureau on 14 April 2011 (14.04.2011)

1. A foamable composition comprising:

a) a short chain alcohol;

b) water;

c) a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof; and

d) a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition;

wherein the foamable composition is surfactant free;
wherein the foamable composition is substantially polymeric agent free;
wherein the percent by weight is based on weight foamable composition;
wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and

wherein upon dispensing the foamable carrier composition forms a foam of quality that is thermally stable at a temperature of 36°C having a collapse time about or more than 60 seconds.

2. The composition of claim 1, wherein the short chain alcohol is selected from the group consisting of ethanol or isopropanol.

3. The composition of claim 1, wherein the foaming booster combination is a synergistic combination that can improve the foam quality and or thermal stability of the composition.

4. The composition of claim 1, further comprising at least one active agent

5. The composition of claim 4, wherein the active agent is selected form the group consisting of an active herbal extract, an acaricides, an age spot and keratose removing agent, an allergen, an alpha hydroxyl acid, an analgesic agent, an anesthetic, an immunogenic substance, an antiacne agent, an antiallergic agent, an antiaging agent, an antibacterial agent, an antibiotic, an antiburn agent, an anticancer agent, an antidandruff agent, an antidepressant, an antidermatitis agent, an antiedemic anent, an antifungal agent, an antihistamine, an antihelminth agent, an antihyperkeratolyte agent, an anti-infective agent, an antiinflammatory agent, ań antiirritant, an antilipemic agent, an antimicrobial agent, an antimycotic agent, an

antioxidant, an antiparasitic agent, an anti-pigmentation agent, an antiproliferative agent, an antipruritic agent, an antipsoriatic agent, an antirosacea agent, an antiseborrheic agent, an antiseptic agent, an antiswelling agent, an antiviral agent, an anti-wart agent, an anti-wrinkle agent, an antiyeast agents, an astringent, a beta-hydroxy acid, benzoyl peroxide, benzoyl chloride a, topical cardiovascular agent, a chemotherapeutic agent, a corticosteroid, an immunogenic substance, a dicarboxylic acid, a disinfectant, a fungicide, a hair growth regulator, a haptene, a hormone, a hydroxy acid, an immunosuppressant, an immunoregulating agent, an immunomodulator, an insecticide, an insect repellent, a keratolytic agent, a lactam, a local anesthetic agent, a lubricating agent, a masking agent, a metals, a metal oxide, a mitocide, a neuropeptide, a non-steroidal anti-inflammatory agent, an oxidizing agent, a pediculicide, a peptide, a protein, a photodynamic therapy agent, a radical scavenger, a refatting agent, a retinoid, a sanative, a scabicide, a self tanning agent, silicone talc, a skin protective agent, a skin whitening agent, a steroid, a steroid hormone, a steroidal antiinflammatory agent ,a vasoconstrictor, a vasodilator, a vitamin, a vitamin A, a vitamin A derivative, a vitamin B, a vitamin B derivative, a vitamin C, a vitamin C derivative, a vitamin D, a vitamin D derivative, a vitamin D analog, a vitamin F, a vitamin F derivative, a vitamin K, a vitamin K derivative, a wound healing agent and a wart remover and mixtures thereof.

6. The composition of claim 1, wherein the composition is transparent upon pressurization by the gas propellant.

7. The composition of claim 1, wherein the composition further includes about 0.1% to about 5% of a humectant.

8. The composition of claim 7, wherein the humectant is selected from the group consisting of PEG 400, propylene glycol and glycerin.

9. The composition of claim 1, wherein the composition is essentially polymer free.

10. The composition of claim 1, wherein the fatty acid or fatty alcohol is selected from the group consisting of (i) 14 to 18 carbon atoms in its carbon chain or (ii)16 to 18 carbon atoms in its carbon chain.

11. The composition of claim 3, wherein the synergistic combination is of at least two fatty alcohols.

12. The composition of claim 11, wherein the combination of fatty alcohols is selected form a group comprising (i) a stearyl alcohol and cetyl alcohol or (ii) cetyl alcohol and myristyl alcohol.

13. The composition of claim 1, wherein the foaming booster is between about 1% and about 10% by weight of the composition.

14. The composition of claim 11, wherein the ratio between at least two fatty alcohols is between about 11:5 and about 5:11.

15. The composition of claim 11, wherein the ratio between at least two fatty alcohols is about 1:1.

16. The composition of claim 1, wherein the short chain alcohol is selected from the group consisting of (i) at least about 15% by weight of the composition or (ii) is between about 20% and 60% by weight of the composition or (iii) is between about 30% and 60% by weight of the composition or (iv) is between about 40% and 60% by weight of the composition.

17. The composition of claim 1, which is thermally stable at 36 °C having a collapse time of about or more than 120 seconds.

18. The composition of claim 1, which is thermally stable at 36 °C having a collapse time of about or more than 180 seconds.

19. The composition of claim 1, further comprising a hydrophilic solvent.

20. The composition of claim 1, wherein the short chain alcohol is replaced by a hydrophilic solvent.

21. The composition of claim 1, wherein the foam is a breakable foam that is thermally stable upon dispensing yet breaks easily upon application of shear force.

22. The foamable composition of claim 1, wherein the foamable composition comprises 0% to 0.2% polymeric agent.

23. A foamable composition comprising:

a) a short chain alcohol;

b) water;

c) a foaming booster comprising at least one fatty alcohol or at least one fatty acid or a combination thereof or a synergistic combination of two or more fatty alcohols; and

d) a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition;

wherein the foamable composition is surfactant free;
wherein the foamable composition is substantially polymeric agent free;
wherein the percent by weight is based on weight foamable composition;
wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and
wherein the ratio between the two fatty alcohols is between about 11:5 and about 5:11.

24. The foamable composition of claim 23, wherein the ratio between the two fatty alcohols is about 1:1.

25. The foamable composition of claim 23, further comprising an active agent.

26. The foamable composition of claim 23, wherein the foamable composition comprises 0% to 0.2% polymeric agent

27. A method of preventing or ameliorating or eliminating or treating or alleviating a dermatological or a mucosal disorder, the method comprising:

applying a foamable composition to a surface having the dermatological or mucosal disorder in need of treatment, said foamable composition comprising:

a) a short chain alcohol;

b) water;

c) a foaming booster comprising at least one fatty alcohol or at least one fatty acid or combination thereof or a synergistic combination of two or more fatty alcohols; and

d) a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition;

wherein the foamable composition is surfactant free;
wherein the foamable composition is substantially polymeric agent free;
wherein the percent by weight is based on weight foamable composition;

wherein the ratio of composition other than propellant to propellant is from about 100:3 to about 100:30; and

wherein upon dispensing the foamable carrier composition forms a foam that is thermally stable at a temperature of 36°C having a collapse time of about or more than 60 seconds.

28. The method of claim 27, further comprising at least one active agent.

29. The method of claim 27, wherein the foamable composition comprises 0% to 0.2% polymeric agent.

30. The use of a foamable composition in the manufacture of a medicament for preventing or treating a dermatological or a mucosal disorder, the foamable composition comprising:

a) a short chain alcohol;

b) water;

c) a foaming booster comprising

d) at least one fatty alcohol or at least one fatty acid or a combination thereof; and

e) a liquefied or compressed gas propellant at a concentration of about 3% to about 30% by weight of the total composition;

wherein the foamable composition is surfactant free;

wherein the foamable composition is substantially polymeric agent free;

wherein the percent by weight is based on weight foamable composition;

wherein the ratio range of composition other than propellant to propellant is from about 100:3 to about 100:30; and

wherein upon dispensing the foamable composition forms a foam of quality that is thermally stable at a temperature of 36°C having a collapse time about or more than 60 seconds.

31. The use of claim 30, further comprising at least one active agent.

32. The use of claim 30, wherein the foamable composition comprises 0% to 0.2% polymeric agent.