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**Tamarkin et al.**(10) **Pub. No.: US 2015/0098907 A1**(43) **Pub. Date: Apr. 9, 2015**(54) **FOAMABLE COMPOSITION AND USES  
THEREOF***A01N 25/16* (2006.01)*A61K 45/06* (2006.01)(71) Applicant: **Foamix Pharmaceuticals Ltd.**, Rehovot  
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Eini**, Ness Ziona (IL)*A61Q 19/02* (2006.01)*A61Q 17/00* (2006.01)*A01N 53/00* (2006.01)*A61K 9/12* (2006.01)(21) Appl. No.: **14/515,715**(52) **U.S. Cl.**(22) Filed: **Oct. 16, 2014**CPC ..... *A01N 25/06* (2013.01); *A01N 53/00*  
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(2013.01); *A01N 25/16* (2013.01)**Related U.S. Application Data**(63) Continuation of application No. 13/400,330, filed on  
Feb. 20, 2012, now Pat. No. 8,900,554, which is a  
continuation of application No. 11/481,596, filed on  
Jul. 6, 2006, now Pat. No. 8,119,150, which is a con-  
tinuation-in-part of application No. 10/532,618, filed  
on Dec. 22, 2005, filed as application No. PCT/  
IB2003/005527 on Oct. 24, 2003, said application No.  
11/481,596 is a continuation-in-part of application No.  
10/911,367, filed on Aug. 4, 2004.(60) Provisional application No. 60/696,878, filed on Jul. 6,  
2005, provisional application No. 60/429,546, filed on  
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The present invention provides a safe and effective insecti-  
cide composition suitable for treating a subject infested with  
a parasitic arthropod or to prevent infestation by an arthro-  
pod. The insecticide composition is a foamable composition,  
including a first insecticide; at least one organic carrier  
selected from a hydrophobic organic carrier, a polar solvent,  
an emollient and mixtures thereof, at a concentration of about  
2% to about 5%, or about 5% to about 10%; or about 10% to  
about 20%; or about 20% to about 50% by weight; about  
0.1% to about 5% by weight of a surface-active agent; about  
0.01% to about 5% by weight of at least one polymeric agent  
selected from a bioadhesive agent, a gelling agent, a film  
forming agent and a phase change agent; and (5) a liquefied or  
compressed gas propellant at a concentration of about 3% to  
about 25% by weight of the total composition.

## FOAMABLE COMPOSITION AND USES THEREOF

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 13/400,330, filed on Feb. 20, 2012, entitled Foamable Composition and Uses thereof, which is a continuation of U.S. patent application Ser. No. 11/481,596, filed on Jul. 6, 2006, entitled Non-Flammable Insecticide Composition and Uses thereof, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Patent Application Ser. No. 60/696,878, filed on Jul. 6, 2005, entitled “Non-Flammable Insecticide Composition and Uses Thereof.”

[0002] U.S. patent application Ser. No. 11/481,596 is also a continuation-in-part application of U.S. patent application Ser. No. 10/532,618, filed on Dec. 22, 2005, which is a 371 application of International Patent Application No. IB03/005527, designating the United States and filed on Oct. 24, 2003, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Patent Application Ser. No. 60/429,546, filed on Nov. 29, 2002, both entitled “Cosmetic and Pharmaceutical Foam,” and which claims the benefit of priority under 35 USC § 119(a) to Israeli Patent Application No. 152486, filed Oct. 25, 2002.

[0003] U.S. patent application Ser. No. 11/481,596 is also a continuation-in-part application of co-pending U.S. patent application Ser. No. 10/911,367, filed on Aug. 4, 2004, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Patent Application Ser. No. 60/492,385, filed on Aug. 4, 2003, both entitled “Foam Carrier Containing Amphiphilic Copolymer Gelling Agent”.

[0004] Each of the above applications are incorporated by reference in their entirety herein.

### BACKGROUND OF THE INVENTION

[0005] This invention relates to foamed insecticide compositions.

[0006] An insecticide is a compound used to kill or prevent the growth of parasite arthropods, such as insects and/or arachnids and/or crustacean; or a compound used to repel or prevent infestation by parasite arthropods, such as insects and/or arachnids and/or crustacean. Common infestations in humans include lice and scabies.

[0007] Infestation with lice is referred to as pediculosis. Lice are ectoparasites that live on the body. The 3 types of lice that parasitize humans are *Pediculus humanus capitis* (head louse), *Pediculus humanus corporis* (body louse), and *Phthirus pubis* (pubic louse).

[0008] Every year, between six and 12 million people in the United States, primarily children three to 10 years of age, are infested with head lice. Girls are at greater risk because they have more frequent head-to-head contact. Head lice affect people across the socioeconomic spectrum.

[0009] Scabies is an infestation of the skin with the microscopic mite *Sarcoptes scabiei*. Infestation is common, found worldwide, and affects people of all races and social classes. Scabies spreads rapidly under crowded conditions where there is frequent skin-to-skin contact between people, such as in hospitals, institutions, child-care facilities, and nursing homes.

[0010] Occasionally, a skin infection develops following a bite. Scratching as a result of insect bites can damage the skin

and allow bacteria to get in. Infection causes redness and tenderness around the bite, which may gradually spread, and sometimes can become serious.

[0011] Resistance of insects to pesticides is commonly known. For example, resistance of lice to 1 percent permethrin has been reported in the US and elsewhere. There are two broad mechanisms by which insect pests develop resistance to insecticides. They may produce large amounts of enzymes, such as esterases which either break down the insecticide molecule or bind to it so tightly that it cannot function (a process known as sequestration). The second mechanism involves mutation of the insecticide target site, such as the acetylcholinesterase enzyme in the nervous system. This effectively blocks the action of the insecticide. Both types of mechanism have been studied in various species of insect.

[0012] A common way to overcome resistance is to add a secondary active agent, which impedes that resistance mechanism. An example of such secondary active agent is piperonyl butoxide, which inhibits the ability of insects to degrade insecticides such as pyrethrum. Another approach is to add volatile solvents such as ethanol and propanol to the insecticide formulation.

[0013] U.S. Pat. No. 5,783,202 provides a pediculicidal mousse composition containing (a) from about 0.1 to about 10% w/w of a pediculicidal agent, preferably, pyrethrin, and, optionally from about 0.5 to about 15% w/w of a synergizer therefor, such as piperonyl butoxide, (b) about 70 to about 97% w/w of a foaming agent, which is preferably a quick breaking alcoholic foaming agent; and (c) from about 3 to about 20% w/w of an aerosol propellant.

[0014] A pediculocide mousse, which contains the active ingredients piperonyl butoxide (4%) and pyrethrum (0.33%) and the inactive ingredients cetearyl alcohol, isobutane, PEG-20 stearate, propane, propylene glycol, purified water, quaternium-52, SD Alcohol 3-C (26.5% w/w) is commercially available under the name “RID Lice Killing Mousse” (Bayer Corporation). However, this product possesses at least four disadvantages: (1) Irritability: due to the high alcohol content, the incidence of skin and eye irritation is high; (2) “Quick breaking” property: the foam is thermo-sensitive and breaks down rapidly at body temperature so that it cannot easily be spread manually throughout the scalp area; (3) Skin drying; and (4) Inflammability: 26.3% alcohol renders the foam inflammable. A test according to European Standard prEN 14851, titled “Aerosol containers—Aerosol foam flammability test” reveals that this product is inflammable.

[0015] Thus, the development of new formulations of permethrin, which will overcome these and other disadvantages, is warranted.

[0016] Furthermore, an easy to use product that addresses the frequent skin and eye irritation associated with pediculocide shampoo, cream rinses and lotions is highly desirable.

### SUMMARY OF THE INVENTION

[0017] The present invention provides a safe and effective insecticide composition. In one aspect, the composition of the present invention is suitable for treating a subject infested with a parasite preventing infestation by a parasite. In some embodiments, the parasite is an arthropod.

**[0018]** In one or more embodiments, the insecticide composition is a foamable composition, including:

**[0019]** (1) a first insecticide;

**[0020]** (2) at least one organic carrier selected from a hydrophobic organic carrier, a polar solvent, an emollient and mixtures thereof, at a concentration of about 2% to about 5%, or about 5% to about 10%; or about 10% to about 20%; or about 20% to about 50% by weight;

**[0021]** (3) a surface-active agent;

**[0022]** (4) about 0.01% to about 5% by weight of at least one polymeric agent selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and

**[0023]** (5) a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

**[0024]** In another aspect of the present invention, an insecticide composition includes:

**[0025]** (i) a first insecticide;

**[0026]** (ii) an organic carrier, at a concentration of about 5% to about 50%, said organic carrier containing at least one member selected from the group of (1) a second insecticide comprising a plant-derived oil having the ability to kill or prevent the growth of parasite arthropods or to repel or prevent infestation by parasite arthropods, and (2) a potent solvent; and

**[0027]** (iii) a surface-active agent.

**[0028]** In a further embodiment, the insecticide composition contains both (1) a second insecticide, for example, a plant-derived oil having the ability to kill or prevent the growth of parasite arthropods or to repel or prevent infestation by parasite arthropods, and (2) a potent solvent.

**[0029]** In further embodiments, the insecticide is an emulsion, for example, an oil-in-water emulsion.

**[0030]** In still other embodiments, a therapeutic kit provides a safe and effective dosage of an insecticide. The kit includes an aerosol packaging assembly including a container accommodating a pressurized product, and an outlet capable of releasing the pressurized product as a foam. The pressurized product is any of the foamable compositions described herein.

**[0031]** Water and optional ingredients are added to complete the total mass to 100%. All % values are provided on a weight (w/w) basis. Upon release from an aerosol container, the foamable composition forms an expanded foam suitable for topical administration.

#### DETAILED DESCRIPTION OF THE INVENTION

**[0032]** The foamable insecticide composition is contained in an aerosol container. Upon release from an aerosol container, the foamable composition forms an expanded foam suitable for the treatment of bodies and surfaces.

**[0033]** According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butanol, isobutanol, t-butanol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. This disadvantage is particularly meaningful in the case of an insecticide treatment, which is often directed to sensitive and damaged skin and mucosal tissues. Thus, in one or more embodiments, the composition is substantially alcohol-free

and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

#### Insecticide

**[0034]** In the context of one or more embodiments of the present invention, an insecticide is a compound used to kill or prevent the growth of parasite arthropods, such as insects, arachnids and crustaceans, or a compound used to repel or prevent infestation by these parasite arthropods.

**[0035]** In one or more embodiments, the insecticide is an antibiotic insecticide. Examples of antibiotic insecticides include allosamidin, thuringiensin, spinosad, avermectin insecticides, such as abamectin, doramectin, emamectin, eprinomectin, ivermectin and selamectin, milbemycin insecticides, such as lepipsectin, milbemectin, milbemycin oxime and moxidectin, and arsenical insecticides.

**[0036]** In one or more embodiments, the insecticide is a botanical insecticide, such as anabasine, azadirachtin, d-limonene, nicotine, pyrethrins, cinerins, jasmolin, quassia, rotenone, ryania and sabadilla.

**[0037]** In one or more embodiments, the insecticide is a carbamate insecticide. Examples of carbamate insecticides include bendiocarb, carbaryl, benzofuranyl methylcarbamate insecticides, such as benfuracarb, carbofuran, carbosulfan, decarbofuran and furathiocarb, dimethylcarbamate insecticides, such as dimetan, dimetilan, hyquincarb and pirimicarb, oxime carbamate insecticides, such as alanycarb, aldycarb, aldoxycarb, butocarboxim, butoxycarboxim, methomyl, nitrilacarb, oxamyl, tazimcarb, thiocarboxime, thiodicarb and thiofanox, and phenyl methylcarbamate insecticides, such as allylcarb, aminocarb, bufencarb, butacarb, carbanolate, cloethocarb, dicresyl, dioxacarb, ethiofencarb, fenethacarb, fenobucarb, isoprocacarb, methiocarb, metolcarb, mexacarb, promacyl, promecarb, propoxur, trimethacarb and xylcarb.

**[0038]** In one or more embodiments, the insecticide is a dinitrophenol insecticides. Examples of dinitrophenol insecticides include dinex, dinoprop and dinosam.

**[0039]** In one or more embodiments, the insecticide is a fluorine insecticide, such as barium hexafluorosilicate, cryolite, sodium fluoride, sodium hexafluorosilicate and sulfluramid.

**[0040]** In one or more embodiments, the insecticide is a formamidine insecticide, such as amitraz, chlordimeform, formetanate and formparanate.

**[0041]** In one or more embodiments, the insecticide is an insect growth regulator. Examples of insect growth regulators include chitin synthesis inhibitors, such as bistrifluron, buprofezin, chlorfluazuron, cyromazine, diflubenzuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, nov-aluron, noviflumuron, penfluron, teflubenzuron and triflumuron, juvenile hormone mimics, such as epofenonane, fenoxycarb, hydroprene, kinoprene, methoprene, pyriproxyfen and triprene, juvenile hormones, moulting hormone agonists, such as chromafenozide, halofenozide, methoxyfenozide and tebufenozide, moulting hormones, such as  $\alpha$ -ecdysone and ecdysterone, moulting inhibitors, such as diofenolan, precocenes, and dicyclanil.

**[0042]** In one or more embodiments, the insecticide is a nereistoxin analogue insecticide, such as bensultap, cartap, thiocyclam and thiosultap.

**[0043]** In one or more embodiments, the insecticide is a nicotinoid insecticide. Examples of nicotinide insecticides

include flonicamid, nitroguanidine insecticides, such as clothianidin, dinotefuran, imidacloprid and thiamethoxam, nitromethylene insecticides, such as nitenpyram and nithiazine, and pyridylmethanimine insecticides, such as acetamiprid, imidacloprid, nitenpyram and thiacloprid.

**[0044]** In one or more embodiments, the insecticide is an organochlorine insecticide. Examples of organochlorine insecticides include bromo-DDT, camphechlor, DDT, lindane, methoxychlor, pentachlorophenol, cyclodiene insecticides, such as aldrin, bromocyclen, chlorbicyclen, chlordane, chlordecone, dieldrin, dilor, endosulfan, endrin, heptachlor, isobenzan, isodrin, kelevan and mirex.

**[0045]** In one or more embodiments, the insecticide is an organophosphorus insecticide. Examples of organophosphorus insecticides include organophosphate insecticides such as bromfeninfos, chlorfeninfos, crotoxyphos, dichlorvos, dicrotophos, dimethylvinphos, fospirate, heptenophos, methocrotophos, mevinphos, monocrotophos, naftalofos, phosphamidon, propaphos and tetrachlorvinphos, organothiophosphate insecticides, such as dioxabenzofos, fosmethilan, phenthoate, acethion, amiton, cadusafos, chlorethoxyfos, chlormephos, demephion, demephion, demeton, disulfoton, ethion, ethoprophos, isothioate, malathion, methacrifos, oxydemeton-methyl, oxydeprofos, oxydisulfoton, phorate, sulfotep, terbufos and thiometon, aliphatic amide organothiophosphate insecticides, such as amidithion, cyanthoate, dimethoate, ethoate-methyl, formothion, mecarbam, omethoate, prothoate, sophamide and vamidothion, oxime organothiophosphate insecticides, such as chlorphoxim, phoxim and phoxim-methyl, heterocyclic organothiophosphate insecticides, such as azamethiphos, coumaphos, coumithoate, dioxathion, endothion, menazon, morphothion, phosalone, pyraclofos, pyridaphenthion and quinothion, benzothioopyran organothiophosphate insecticides, such as dithicrofos and thicrofos, benzotriazine organothiophosphate insecticides, such as azinphos-ethyl and azinphos-methyl, isoindole organothiophosphate insecticides, such as dialifos and phosmet, isoxazole organothiophosphate insecticides, such as isoxathion and zolaprofos, pyrazolopyrimidine organothiophosphate insecticides, such as chlorprazophos and pyrazophos; pyridine organothiophosphate insecticides, such as chlorpyrifos and chlorpyrifos-methyl, pyrimidine organothiophosphate insecticides, such as butathiofos, diazinon, etrimfos, lirimfos, pirimiphos-ethyl, pirimiphos-methyl, primidophos, pyrimitate and tebupirimfos, quinoxaline organothiophosphate insecticides, such as quinalphos and quinalphos-methyl, thiadiazole organothiophosphate insecticides, such as athidathion, lythidathion, methidathion and prothidathion, triazole organothiophosphate insecticides, such as isazofos and triazophos, phenyl organothiophosphate insecticides, such as azothoate, bromophos, bromophos-ethyl, carbophenothion, chlorthiophos, cyanophos, cythioate, dicapthion, dichlofenthion, etaphos, famphur, fenchlorphos, fenitrothion, fensulfathion, fenthion, fenthion-ethyl, heterophos, jodfenphos, mesulfenfos, parathion, parathion-methyl, phenkapton, phosnichlor, profenofos, prothiofos, sulprofos, temephos, trichlormetaphos-3 and trifenofos, phosphonate insecticides, such as butonate and trichlorfon, phosphonothioate insecticides such as mecarphon, phenyl ethylphosphonothioate insecticides, such as fonofos and trichloronat, phenyl phenylphosphonothioate insecticides, such as cyanofenphos, EPN and leptophos, phosphoramidate insecticides, such as crufomate, fenamiphos, fosthietan, mephosfolan, phosfolan and pirimetaphos, phosphoramidothioate

insecticides, such as acephate, isocarbophos, isofenphos, methamidophos and propetamphos, and phosphorodiamide insecticides, such as dimefox, mazidox, mipafox and schradan.

**[0046]** In one or more embodiments, the insecticide is an oxadiazine insecticide, such as indoxacarb.

**[0047]** In one or more embodiments, the insecticide is a phthalimide insecticide, such as dialifos, phosmet and tetramethrin.

**[0048]** In one or more embodiments, the insecticide is a pyrazole insecticide, such as acetoprole, ethiprole, fipronil, pyrafluprole, pyriprole, tebufenpyrad, tolfenpyrad and vaniliprole.

**[0049]** In one or more embodiments, the insecticide is a pyrethroid insecticide. Examples of pyrethroid insecticides include pyrethroid ester insecticides, such as acrinathrin, allethrin, bioallethrin, barthrin, bifenthrin, bioethanomethrin, cyclothrin, cycloprothrin, cyfluthrin, beta-cyfluthrin, cyhalothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, theta-cypermethrin, zeta-cypermethrin, cyphenothrin, deltamethrin, dimethrin, empenthrin, fenfluthrin, fenpirithrin, fenpropathrin, fenvalerate, esfenvalerate, flucythrinate, fluvalinate, furethrin, imiprothrin, metofluthrin, permethrin, biopermethrin, transpermethrin, phenothrin, prallethrin, profluthrin, pyresmethrin, resmethrin, bioresmethrin, cismethrin, tefluthrin, terallethrin, tetramethrin, tralomethrin and transfluthrin, and pyrethroid ether insecticides, such as etofenprox, flufenprox, halfenprox, protrifenbutate and silafluofen.

**[0050]** In one or more embodiments, the insecticide is a pyrimidinamine insecticide, such as flufenimer and pyrimidifen.

**[0051]** In one or more embodiments, the insecticide is a pyrrole insecticide, such as chlorfenapyr.

**[0052]** In one or more embodiments, the insecticide is a tetrone acid insecticide, such as spiromesifen and spirotetramat.

**[0053]** In one or more embodiments, the insecticide is a thiourea insecticide, such as diafenthion.

**[0054]** In one or more embodiments, the insecticide is a urea insecticide, such as flucifuron and sulcifuron.

**[0055]** Yet, in additional embodiments, the insecticide is an unclassified insecticide, such as closantel, crotamiton, fenazaflor, fenoxacrim, flubendiamide, hydramethylnon, isoprothiolane, malonoben, metaflumizone, metoxadiazole, nifluridide, pyridaben, pyridalyl, rafoxanide, triarathene and triazamate.

**[0056]** The above listed insecticides, as well as others not listed, are suitable for use in the composition of the present invention. It is preferred to use insecticides that are approved by the FDA or other health authorities for the treatment of animals and humans.

**[0057]** Non-limiting examples of approved insecticides include hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, bioallethrin, phenothrin, malathion and piperonyl butoxide. In a preferred embodiment of the present invention the insecticide is selected from the group consisting of hexachlorobenzene, carbamate, naturally occurring pyrethroids, permethrin, allethrin, bioallethrin, phenothrin, malathion and piperonyl butoxide.

**[0058]** In one or more embodiments, the insecticide is a naturally occurring insecticide compound. As used herein,

the term “naturally-occurring insecticide” includes all insecticides that are obtained, derived or extracted from plant or vertebrate sources.

**[0059]** In the context of the present invention, an agent that kills or otherwise affects parasites, such as protozoa is also termed an insecticide (for the purpose of this application terminology only). Exemplary antiparasites are mebendazole, thiabendazole, metronidazole, and praziquantel.

**[0060]** Mixtures of these insecticides may also be employed according to the present invention.

**[0061]** The insecticide is included in the composition of the present invention in a concentration that provides a desirable ratio between the efficacy and safety. Typically, insecticides are included in the composition in a concentration between about 0.05% and about 12% by weight, depending on their potency against the parasitic arthropod to be eradicated. In some embodiments, the concentration is between about 0.5% and about 2% by weight; in other embodiment the concentration is between about 2% and about 5% by weight; and in other embodiments the concentration is between about 5% and about 12% by weight.

**[0062]** In one or more embodiments, the insecticide is encapsulated in particles, microparticles, nanoparticles, microcapsules, spheres, microspheres, nanocapsules, nanospheres, liposomes, niosomes, polymer matrix, nanocrystals or microsponges, and may be manufactured according to known methods.

#### Organic Carrier

**[0063]** The foamable composition of the present invention can be an emulsion, or microemulsion, including an aqueous phase and an organic carrier phase. The organic carrier is selected from a hydrophobic organic carrier (also termed herein “hydrophobic solvent”), an emollient, a solvent, and a mixture thereof.

**[0064]** A “hydrophobic organic carrier” as used herein refers to a material having solubility in distilled water at ambient temperature of less than about 1 gm per 100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL. It is liquid at ambient temperature. The identification of a hydrophobic organic carrier or “hydrophobic solvent”, as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a hydrophobic carrier in the foamable compositions described herein.

**[0065]** In one or more embodiments, the hydrophobic organic carrier is an oil, such as mineral oil. According to one or more embodiments, the hydrophobic solvent is a liquid oil originating from vegetable, marine or animal sources. Suitable liquid oil includes saturated, unsaturated or polyunsaturated oils. Another class of hydrophobic solvents is the essential oils. Silicone oils also may be used and are desirable due to their known skin protective and occlusive properties.

**[0066]** A further class of organic carriers includes “emollients” that have a softening or soothing effect, especially when applied to body areas, such as the skin and mucosal surfaces. Emollients are not necessarily hydrophobic. Examples of suitable emollients include hexyleneglycol, propylene glycol, isostearic acid derivatives, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate,

cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, propylene glycol ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, sucrose esters of fatty acids, octyl hydroxystearate and mixtures thereof.

**[0067]** In an embodiment of the present invention, the organic carrier is a polypropylene glycol alkyl ether (PPG alkyl ether). PPG alkyl ethers are liquid, water-insoluble propoxylated fatty alcohols, having the molecular formula of  $\text{RO}(\text{CH}_2\text{CHOCH}_3)_n$ , wherein “R” is a straight-chained or branched  $\text{C}_4$  to  $\text{C}_{22}$  alkyl group; and “n” is in the range between 4 and about 50. They are organic liquids that function as skin-conditioning agent in pharmaceutical and cosmetic formulations. Non-limiting exemplary PPG alkyl ethers include PPG stearyl ethers and PPG butyl ether. Preferred PPG alkyl ethers according to the present invention include PPG-15 stearyl ether, PPG-2 butyl ether, PPG-9-13 butyl ether and PPG-40 butyl ether.

**[0068]** According to a preferred embodiment, the organic carrier does not contain petrolatum, which is also referred to as “white petrolatum” or Vaseline. Petrolatum often forms an impermeable occlusive barrier, so that metabolic products and excreta from damaged tissue are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the treated tissue, so the efficacy of the drug is reduced. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds causing inconvenience to the user, thereby decreasing treatment compliance.

**[0069]** In one or more embodiments, the organic carrier contains a plant-derived oil, which possesses insecticide properties, i.e., a plant derived oil that has the ability to kill or prevent the growth of parasite arthropods or to repel or prevent infestation by parasite arthropods (herein referred to as a “second hydrophobic insecticide” or “plant derived insecticide”).

**[0070]** Examples of plant-derived insecticides include but are not limited to the oils of anise, bergemont, canola, cassia, catnip, cedarwood, citronella, clove, eucalyptus, garlic, ginger, grapefruit, jojoba, lavender, lavandin, lemon, lime, orange, peppermint, rosemary, sage, spearmint, star anise, tea tree, tangerine, thyme and white clover.

**[0071]** In one or more embodiments, the “second insecticide” agent is an insect repellent. In one or more embodiment, the insect repellent is a chemical insect repellent, such as diethyl toluamide (DEET). In one or more embodiments, the insect repellent is a naturally-derived insect repellent.

**[0072]** In one or more embodiments, the insect repellent is repellents that include terpenoid compounds, as described in U.S. Pat. No. 5,411,992, including:

**[0073]** (1) Terpenoid-alcohol or terpene-ols are terpenoids which have at least one hydroxyl group. Examples of terpene-ols include:  $\text{C}_{10}\text{H}_{16}\text{O}$  compounds, perillyl alcohol, carveol, myrtenol, and cis-verbenol;  $\text{C}_{10}\text{H}_{18}\text{O}$  compounds, myrtenol, iso-pinocampheol, dihydrocarveol, isopulegol, terpineol, terpinen-4-ol, nerol, geraniol, and linalool, and  $\text{C}_{10}\text{H}_{20}\text{O}$  compounds, menthol, beta-citronellol, and dihydro-myrcenol.

**[0074]** (2) Terpenoid-esters are terpenoids, which have at least one ester group which is the product of the bonding of the hydroxyl group of a terpene-ol with an aliphatic carboxylic acid that can contain functional groups such as the hydroxyl or amine on the aliphatic chain. Examples of suitable aliphatic carboxylic acids include acetic acid, propionic acid, lactic acid, and various amino acids. Examples of terpenoid-esters include carvyl acetate, carvyl propionate, and menthyl lactate.

**[0075]** (3) Essential oils which contain terpenoids and perfumes which contain terpenoids. Non-limiting examples of essential oils which have high content of terpene-ols and esters include bergamot (62% terpenoids); sage (>50% terpenoids); styrax (>50% terpenoids); peppermint (>50% terpenoids); and pine Siberian (75% terpenoids).

**[0076]** Combining a first insecticide and a second insecticide having different mechanisms of action provides an enhanced and conceivably a synergistic effect against the parasitic arthropods.

#### Potent Solvent

**[0077]** In one or more embodiments, the organic carrier contains at least one solvent having a high solubilization capacity, termed herein a "potent solvent". In the context of the present invention, a potent solvent is a solvent, other than a short chain alcohol or water, that solubilizes the first and/or second insecticide.

**[0078]** In one or more embodiments, the potent solvent is selected from the group consisting of a polyol, propylene glycol, hexylene glycol, butanediol, diethylene glycol, benzyl alcohol, terpenes, di-terpenes, limonene, terpene-ol, dioxolane, dimethylformamide, dimethyl sulfoxide (DMSO), methyl dodecyl sulfoxide, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, isosorbide derivatives, dimethyl isosorbide, glycofurol and ethoxydiglycol (transcutol) and mixtures thereof in any proportion.

**[0079]** Combining a first insecticide and a potent solvent increase penetration of the insecticide to its target site of action and dissolves the cuticle of the arthropod or the outer surface of the nits, thereby providing an enhanced and conceivably a synergistic effect against the parasitic arthropods.

**[0080]** In one or more embodiments, the organic carrier contains both a second insecticide and a potent solvent. The combination of a first insecticide, a second insecticide and a potent solvent in combination provides an exceptionally effective product for the treatment of parasitic arthropods, as demonstrated in the examples herein.

#### Polymeric Agent

**[0081]** The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ. Exemplary polymeric agents are classified below in a non-limiting manner. In certain cases, a given polymer can belong to more than one of the classes provided below.

**[0082]** In one or more embodiments, the polymeric agent includes at least one gelling agent. A gelling agent controls the residence of a therapeutic composition in the target site of treatment by increasing the viscosity of the composition,

thereby limiting the rate of its clearance from the site. Many gelling agents are known in the art to possess mucoadhesive properties.

**[0083]** The gelling agent can be a natural gelling agent, a synthetic gelling agent and an inorganic gelling agent. Exemplary gelling agents that can be used in accordance with one or more embodiments of the present invention include, for example, naturally-occurring polymeric materials, such as locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, starch, chemically modified starches and the like, semi-synthetic polymeric materials such as cellulose ethers (e.g. hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxypropylmethyl cellulose, hydroxyethylcarboxymethylcellulose, carboxymethylcellulose and carboxymethylhydroxyethylcellulose), guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guar, and the like, and synthetic polymeric materials, such as carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like. Mixtures of the above compounds are contemplated.

**[0084]** Further exemplary gelling agents include the acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers, which consist essentially of a colloidal water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with a crosslinking agent such as polyallyl sucrose or polyallyl pentaerythritol. Examples include Carbopol® 934, Carbopol® 940, Carbopol® 950, Carbopol® 980, Carbopol® 951 and Carbopol® 981.

**[0085]** The polymeric agent can be an inorganic gelling agent, such as silicone dioxide (fumed silica).

**[0086]** In an embodiment of the present invention, the polymeric agent includes at least one mucoadhesive or bioadhesive agent. Mucoadhesive/bioadhesion has been defined as the attachment of synthetic or biological macromolecules to a biological tissue. Mucoadhesive agents are a class of polymeric biomaterials that exhibit the basic characteristic of a hydrogel, i.e. swell by absorbing water and interacting by means of adhesion with the mucous that covers epithelia. Compositions according to one or more embodiments of the present invention may contain a mucoadhesive macromolecule or polymer in an amount sufficient to confer bioadhesive properties. The bioadhesive macromolecule enhances the delivery of biologically active agents on or through the target surface. The mucoadhesive macromolecule may be selected from acidic synthetic polymers, preferably having at least one acidic group per four repeating or monomeric subunit moieties, such as poly(acrylic)- and/or poly(methacrylic) acid (e.g., Carbopol®, Carbomer®), poly(methylvinyl ether/maleic anhydride) copolymer, and their mixtures and copolymers; acidic synthetically modified natural polymers, such as carboxymethylcellulose (CMC); neutral synthetically modified natural polymers, such as (hydroxypropyl)methylcellulose; basic amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid, hyaluronic acid, pectin, gum tragacanth, and karaya gum; and neutral synthetic polymers, such as polyvinyl alcohol or their mixtures. An additional group of mucoadhesive polymers includes natural and chemically modified cyclo-

dextrin, especially hydroxypropyl- $\beta$ -cyclodextrin. Such polymers may be present as free acids, bases, or salts, usually in a final concentration of about 0.01% to about 0.5% by weight. Many mucoadhesive agents are known in the art to also possess gelling properties.

**[0087]** In one or more embodiments, the polymeric agent includes at least one film forming polymer. The film forming component may include at least one water-insoluble alkyl cellulose or hydroxyalkyl cellulose. Exemplary alkyl cellulose or hydroxyalkyl cellulose polymers include ethyl cellulose, propyl cellulose, butyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxybutyl cellulose, and ethyl-hydroxyethyl cellulose, alone or in combination. In addition, a plasticizer or a cross linking agent may be used to modify the polymer's characteristics. For example, esters such as dibutyl or diethyl phthalate, amides such as diethyldiphenyl urea, vegetable oils, fatty acids and alcohols such as oleic and myristyl acid may be used in combination with the cellulose derivative.

**[0088]** In one or more embodiments, the polymeric agent includes at least one phase change polymer, which alters the composition behavior from fluid-like prior to administration to solid-like upon contact with the target mucosal surface. Such phase change results from external stimuli, such as changes in temperature or pH and exposure to specific ions (e.g.,  $\text{Ca}^{2+}$ ). Non-limiting examples of phase change polymers include poly(N-isopropylamide) and Poloxamer 407®.

**[0089]** The polymeric agent is present in an amount in the range of about 0.01% to about 5.0% by weight of the foam composition. In one or more embodiments, it is typically less than about 1 wt % of the foamable composition.

#### Surface Active Agent

**[0090]** Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipophilic balance (HLB) describes the emulsifier's affinity toward water or oil. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). The surface active agent according to the present invention has an HLB value, suitable for stabilizing an emulsion comprising the aqueous phase and the organic carrier of the composition.

**[0091]** According to one or more embodiments of the present invention, the surface-active agent has a hydrophilic lipophilic balance (HLB) between about 9 and about 14, which is the required HLB (the HLB required to stabilize an O/W emulsion of a given oil) of most oils and hydrophobic solvents. Thus, in one or more embodiments, the composition contains a single surface active agent having an HLB value between about 9 and 14, and in one or more embodiments, the composition contains more than one surface active agent and the weighted average of their HLB values is between about 9 and about 14. Yet, in other embodiments, when a water in oil emulsion is desirable, the composition contains one or more surface active agents, having an HLB value between about 2 and about 9.

**[0092]** The surface-active agent is selected from anionic, cationic, nonionic, zwitterionic, amphoteric and ampholytic

surfactants, as well as mixtures of these surfactants. Such surfactants are well known to those skilled in the therapeutic and cosmetic formulation art. Nonlimiting examples of possible surfactants include polysorbates, such as polyoxyethylene (20) sorbitan monostearate (Tween 60) and poly(oxyethylene) (20) sorbitan monooleate (Tween 80); poly(oxyethylene) (POE) fatty acid esters, such as Myrj 45, Myrj 49, Myrj 52 and Myrj 59; poly(oxyethylene) alkyl ethers, such as poly(oxyethylene) cetyl ether, poly(oxyethylene) palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1; sucrose esters, partial esters of sorbitol and its anhydrides, such as sorbitan monolaurate and sorbitan monolaurate; mono or diglycerides, isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

**[0093]** In one or more embodiments of the present invention, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. We have surprisingly found that non-ionic surfactants alone provide foams of excellent quality, i.e. a score of "E" according to the grading scale discussed herein below.

**[0094]** In one or more embodiments, the surface active agent includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1.

**[0095]** In one or more embodiments of the present invention, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1. The resultant foam has a low specific gravity, e.g., less than 0.1 g/ml.

**[0096]** The stability of the composition is especially pronounced when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is between about 9 and about 14.

**[0097]** Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is between about 9 and about 14.

**[0098]** In one or more embodiments of the present invention, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher HLB values.

**[0099]** The total surface active agent is in the range of about 0.1 to about 5% of the composition, and is occasionally less than about 2% or less than about 1%.

### Foam Adjuvant

**[0100]** Optionally, a therapeutically effective foam adjuvant is included in the foamable compositions of the present invention to increase the foaming capacity of surfactants and/or to stabilize the foam. In one or more embodiments of the present invention, the foam adjuvant agent includes fatty alcohols having 15 or more carbon atoms in their carbon chain, such as cetyl alcohol and stearyl alcohol (or mixtures thereof). Other examples of fatty alcohols are arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are especially well suited as foam adjuvant agents. The amount of the fatty alcohol required to support the foam system is inversely related to the length of its carbon chains. Foam adjuvants, as defined herein are also useful in facilitating improved spreadability and absorption of the composition.

**[0101]** In one or more embodiments of the present invention, the foam adjuvant agent includes fatty acids having 16 or more carbon atoms in their carbon chain, such as hexadecanoic acid (C16) stearic acid (C18), arachidic acid (C20), behenic acid (C22), octacosanoic acid (C28), as well as fatty acids with longer carbon chains (up to C50), or mixtures thereof. As for fatty alcohols, the amount of fatty acids required to support the foam system is inversely related to the length of its carbon chain.

**[0102]** In one or more embodiments, a combination of a fatty acid and a fatty ester is employed.

**[0103]** Optionally, the carbon atom chain of the fatty alcohol or the fatty acid may be saturated or unsaturated, branched or unbranched, or hydroxylated or unhydroxylated. The fatty alcohol or the fatty acid may have at least one double bond. A further class of foam adjuvant agent includes a branched fatty alcohol or fatty acid. The carbon chain of the fatty acid or fatty alcohol also can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

**[0104]** Fatty alcohols and fatty acids useful in one or more compositions of the present invention may possess therapeutic properties. 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, anti-infective, antiproliferative and anti-inflammatory properties (see, U.S. Pat. No. 4,874,794). Longer chain fatty alcohols, e.g., tetracosanol, hexacosanol, heptacosanol, octacosanol, triacontanol, etc., are also known for their metabolism modifying properties and tissue energizing properties. Long chain fatty acids have also been reported to possess anti-infective characteristics.

### Additional Therapeutic Agent

**[0105]** Several conditions involve a combination of etiological factors, some of which are related to the arthropod or another parasite infestation (that can be affected by an insecticide); and other etiological factors that require an additional therapeutic modality. For example, pediculosis may involve lice infection as well as secondary infection or inflammation, and therefore combined treatment with an insecticide and an anti-inflammatory agent or an antibiotic agent would be beneficial. Likewise, rosacea, which involves a parasite infection, inflammation and telangiectasia, can benefit from treatment with a combination of metronidazole and an additional thera-

peutic agent, selected from the group consisting of an anti-inflammatory agent, an immunomodulator, an anti-pruritic agent and a vasoconstrictor. Hence, in many cases, the inclusion of an additional therapeutic agent in the composition of the present invention, contributes to the clinical activity of the insecticide. Thus, in one or more embodiments, the composition further includes at least one additional therapeutic agent, in a therapeutically effective concentration.

**[0106]** In one or more embodiments, the at least one additional therapeutic agent is selected from the group consisting of a steroidal anti-inflammatory agent, a nonsteroidal anti-inflammatory drug, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal agent, an antibiotic agent, an antifungal agent, an antiviral agent, an antiparasitic agent, a vasoactive agent, a vasoconstrictor, a vasodilator, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a hapten, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebacic acid, adipic acid, fumaric acid, an insecticide, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, an anti-wrinkle agent, a radical scavenger, a metal oxide (e.g., titanium dioxide, zinc oxide, zirconium oxide, iron oxide), silicone oxide, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent and mixtures thereof.

**[0107]** The composition of the present invention may further optionally include a variety of formulation excipients, which are added in order to fine-tune the consistency of the formulation, protect the formulation components from degradation and oxidation and modify their consistency. Such excipients may be selected, for example, from stabilizing agents, antioxidants, humectants, preservatives, colorant and odorant agents and other formulation components, used in the art of formulation.

### Propellant

**[0108]** Aerosol propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable carrier. The propellant makes up about 3% to about 25 wt % of the foamable carrier. Examples of suitable propellants include volatile hydrocarbons such as butane, propane, isobutane or mixtures thereof, chloro-fluoro carbons (CMOs) non-ozone-depleting and fluorocarbon propellants, such as 1,1,1,2 tetrafluoroethane and 1,1,1,2,3,3,3 heptafluoropropane.

### Composition and Foam Physical Characteristics and Advantages

**[0109]** A pharmaceutical or cosmetic composition manufactured using the foam carrier according to one or more embodiments of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a



mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0110] The foam composition of the present invention creates a stable emulsion having an acceptable shelf-life of at least one year, or at least two years at ambient temperature. Plant-derived oils, potent solvents and hydrocarbon propellants, which are a mixture of low molecular weight hydrocarbons, tend to impair the stability of emulsions. It has been observed, however, that emulsion compositions according to the present invention are surprisingly stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

[0111] 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.

[0112] The foam of the present invention has several advantages, when compared with hydroalcoholic foam compositions, such as described in U.S. Pat. No. 5,783,202:

[0113] (1) Breakability. The foam of the present invention is thermally stable. Unlike hydroalcoholic foam compositions the foam of the present invention is not “quick breaking”, i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally-induced breakability, since it allows comfortable application and well directed administration to the target area.

[0114] (2) Irritability. The insecticide composition of the present invention are non-irritant, as revealed in clinical trials, unlike the high incidence of skin and eye irritation caused by the hydroalcoholic foam.

[0115] (3) Skin drying. Alcohol is known to dry the skin and impair the integrity of the skin barrier. By contrast, the insecticide composition of the present invention is an emulsion, which provides skin refatting and skin barrier building effects.

[0116] (4) Inflammability. Alcohol renders the foam inflammable. A test according to European Standard prEN 14851, titled “Aerosol containers—Aerosol foam flammability test” revealed that compositions according to the present invention are non-inflammable, while the hydroalcoholic foam was inflammable.

[0117] In terms of usability, the foamable composition is most advantageous, as revealed by clinical trials:

[0118] (i) Ease of Application.

[0119] Due to the nature a foam product, Foamix Permethrin 1% Foam was found easier to use in comparison with other products available in the market.

[0120] When foam is released it expands in the hair and reaches every spot where lice can be found. This advantage is particularly meaningful in regards to such difficult to access areas as in the neck and behind the ears.

[0121] Using the product with applicator attached to foam container directly onto the scalp under the hair is very convenient.

[0122] (ii) The Foam is Drip-Free

[0123] The foam is not liquid and therefore is not leaking when applied.

[0124] This allows precise application, without the product being spread on clothes or other parts of the body.

[0125] Not a single case of contact with eyes was recorded throughout the study. (It should be noted that the issue of

contact with eyes is a common problem when treating with shampoo, lotion and spray which usually cause eye irritation and burning.)

[0126] (iii) Patients' Response

[0127] Throughout the study it was evident that children enjoy being treated with foam and therefore do not resist the therapy.

[0128] Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL or less than 0.05 g/mL.

#### Fields of Applications

[0129] The present invention provides safe and effective insecticide compositions, suitable to treat any surface or body, infested with an parasitic anthropode, or to prevent infestation by an arthropod. In one or more embodiments, the insecticide composition can be used to kill or prevent the growth of parasite arthropods, such as insects and/or arachnids and/or crustacean. In one or more embodiments, the insecticide composition can be used to repel parasite arthropods or prevent infestation by parasite arthropods.

[0130] According to one or more embodiments of the present invention, the insecticide composition is intended for administration to an animal or a human subject. In one or more embodiments, the composition is intended to treat the skin, a body surface, a body cavity or a mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum.

[0131] In other embodiments, the insecticide composition is intended for the treatment of plants, infested by arthropods.

[0132] Yet, in additional embodiments, the insecticide composition of bodies or surfaces other than animal, human or botanical subjects.

[0133] The insecticide compositions of the present invention are intended for the treatment of infestation by arthropods, including insects, arachnids and crustaceans. Exemplary arthropods to be treated by the insecticide compositions of the present invention are lice and blowfly larvae, bugs, fleas, gnats, mites, chiggers, punkies, copepods, isopods and barnacles.

[0134] The insecticide compositions of the present invention are intended for the prevention of an insect-transmitted disease, such as typhus, Lyme disease, trench fever, leishmaniasis, malaria and relapsing fever.

[0135] The following examples exemplify the therapeutic compositions and pharmacological compositions and methods described herein. The examples are for the purposes of illustration only and are not intended to be limiting of the invention.

#### EXAMPLE 1

[0136] This example describes a foamable insecticide composition containing permethrin (1% or 5%), or malathion (0.5%). The following compositions were prepared by blending the listed ingredients.

	Foam A % w/w	Foam B % w/w	Foam C % w/w
Permethrin (first insecticide)	1.00	5.00	
Malathion (first insecticide)			0.50
Mineral oil	5.60	5.60	5.60

-continued

	Foam A % w/w	Foam B % w/w	Foam C % w/w
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative	0.25	0.25	0.25
TEA	to pH 5.5	to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

## EXAMPLE 2

[0137] This example describes a foamable insecticide composition containing permethrin (1%), malathion (0.5%) or pyrethrum extract (0.33%)+piperonyl butoxide (4%), as “first insecticide” and diisopropyl adipate and dimethyl isosorbide as potent solvents.

	Foam D % w/w	Foam E % w/w	Foam F w/w
Permethrin (first insecticide)	1.00		
Malathion (first insecticide)		0.50	
Pyrethrum extract (first insecticide)			0.33
Piperonyl butoxide (first insecticide)			4.00
Diisopropyl adipate (potent solvent)	3.00	3.00	3.00
Dimethyl isosorbide (potent solvent)	10.00	10.00	10.00
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative	0.25	0.25	0.25
TEA	to pH 5.5	to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

Notes:

—Depending on the severity of the insect infestation and the target site, the concentration of the permethrin can range between 0.1% and 10%.  
 —Depending on the severity of the insect infestation and the target site, the concentration of malathion can range between 0.1% and 5%.  
 —Depending on the severity of the insect infestation and the target site, the concentration of the pyrethroid extract can range between 0.1% and 10%.

## EXAMPLE 3

[0138] This example describes a foamable insecticide composition, containing permethrin (1%), as “first insecticide” and star anise oil as “second insecticide.”

	Foam G % w/w
Permethrin (first insecticide)	1.00
Isopropyl myristate (potent solvent)	5.60
Star anise oil (second insecticide)	2.00
Glyceryl monostearate	0.45
Diisopropyl adipate	3.00
Xanthan gum	0.25
Methocel K100M	0.25
Polysorbate 80	0.85
PEG-40 stearate	2.50

-continued

	Foam G % w/w
Sodium lauryl sulphate	0.40
Preservative	0.25
TEA	to pH 5.5
Propane/Butane	8.00
Purified water	to 100.00

## EXAMPLE 4

[0139] This example describes a foamable insecticide composition, concurrently containing permethrin (1%), malathion (0.5%) or pyrethrum extract (0.33%)+piperonyl butoxide (4%), as “first insecticide” and star anise oil as “second insecticide”, with or without a potent solvent.

	Foam H % w/w	Foam I % w/w	Foam J % w/w
Permethrin (first insecticide)	1.00		
Malathion (first insecticide)		0.50	
Pyrethrum extract (first insecticide)			0.33
Piperonyl butoxide (first insecticide)			4.00
Diisopropyl adipate (potent solvent)	3.00	3.00	3.00
Dimethyl isosorbide (potent solvent)	10.00	10.00	10.00
Star anise oil (second insecticide)	2.00	2.00	2.00
Isopropyl myristate	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50
Sodium lauryl sulphate	0.40	0.40	0.40
Preservative	0.25	0.25	0.25
TEA	to pH 5.5	to pH 5.5	to pH 5.5
Propane/Butane	8.00	8.00	8.00
Purified water	to 100.00	to 100.00	to 100.00

## EXAMPLE 5

[0140] This example describes an insecticide composition concurrently containing permethrin (1%), or malathion (0.5%), as “first insecticide”; star anise oil as “second insecticide”, with or without a potent solvent.

	Emulsion I % w/w	Emulsion II % w/w	Emulsion III % w/w	Emulsion IV % w/w
Permethrin (first insecticide)	1.00	1.00		
Malathion (first insecticide)			0.50	0.50
Mineral oil				5.60
Diisopropyl adipate (potent solvent)	3.00	3.00		
Dimethyl isosorbide (potent solvent)	10.00		10.00	
Star anise oil (second insecticide)	2.00	2.00	2.00	2.00
Isopropyl myristate	5.60	5.60	5.60	5.60
Glyceryl monostearate	0.45	0.45	0.45	0.45
Xanthan gum	0.25	0.25	0.25	0.25
Methocel K100M	0.25	0.25	0.25	0.25
Polysorbate 80	0.85	0.85	0.85	0.85
PEG-40 stearate	2.50	2.50	2.50	2.50
Preservative	0.25	0.25	0.25	0.25

-continued

	Emulsion I % w/w	Emulsion II % w/w	Emulsion III % w/w	Emulsion IV % w/w
TEA	to pH 5.5	to pH 5.5	to pH 5.5	to pH 5.5
Purified water	to 100.00	to 100.00	to 100.00	to 100.00

## EXAMPLE 6

[0141] This example describes non-occlusive insecticide compositions containing permethrin 5%.

Ingredient	PER 079 % w/w	PER 091 % w/w
Permethrin	5.00	5.00
Mineral oil heavy	22.00	—
Isopropyl myristate	11.00	—
Benzyl alcohol	1.50	1.50
Glyceryl monostearate	0.50	0.50
Ceteareth-20	3.30	3.30
Stearyl alcohol	1.10	1.10
Purified water,	56.75	89.75
Carboxymethyl cellulose	0.55	0.55
Glycerin	3.30	3.30
Total product:	100.00	100.00

Notes:

—Propellant was added to the above compositions at a concentration of 8%.

—The total amount of hydrophobic carrier is in the range between 20% and 40%.

## EXAMPLE 7

[0142] This example describes additional insecticide compositions containing permethrin 5%.

Ingredient Name	PER5-092 % w/w	PER5-093 % w/w	PER5-094 % w/w
Permethrin	5.05	5.05	5.05
PPG 15 stearyl ether	15.00	—	12.00
Isopropyl myristate	5.00	5.00	21.00
Benzyl alcohol	1.50	1.50	1.50
Glyceryl monostearate	0.50	0.50	1.00
Ceteareth-20	3.30	3.30	3.30
Stearyl alcohol	1.10	1.10	1.10
Water, purified	62.70	62.70	51.20
Carboxymethyl cellulose	0.55	0.55	0.55
Glycerin	—	—	3.30
Total product:	100.00	100.00	100.00

## EXAMPLE 8

[0143] This example describes an open study to assess the efficacy, safety and usability of a 1% permethrin foam containing a first insecticide, a second insecticide and a potent solvent, in the treatment of head lice (pediculosis capitis) in pediatric patients.

## Study Objectives

[0144] 1. To assess the efficacy and safety of a 1% Permethrin Foam, in the treatment of head lice (pediculosis capitis) in pediatric patients

[0145] 2. To detect any side effects of the Foamix 1% Permethrin Foam.

[0146] 3. To assess the usability of the product.

## Methodology

[0147] The study was performed as a single center open study.

[0148] All patients' parents gave written informed consent to participate in the study.

[0149] The test article, Foamix 1% Permethrin Foam, was applied by the investigator, using an average quantity of 20 gram per patient, according to hair type (length, thickness, curliness etc), on wet or damp hair. The product penetrates under hair via applicator connected to foam container. The foam was spread onto hair through gentle rubbing in. The product remained in contact with hair for 10 minutes and then was washed off with water and a regular shampoo. The same procedure was repeated after 10 days.

[0150] 24 hours after the first treatment, patients were examined for lice visually and by 2-3 minutes combing. Lice and nits found were counted and recorded.

[0151] Dermal side effects (itching, pain, irritation, etc), along with any other adverse events were recorded throughout the study period.

[0152] Number of Patients: 56

## Diagnosis and Main Criteria for Inclusion

[0153] Healthy male and female pediatric patients, 3 and 15 years of age, diagnosed as having pediculosis capitis.

[0154] Test Article: Foam H of Example 4.

[0155] Dose: About 20 gr.

## Mode of Administration

[0156] The treatment was performed by the Investigator or by one of the staff member, under the Investigator's supervision an average quantity of 20 gr. per patient, according to hair type (length, thickness, curliness, etc), on wet or damp hair (after a 2-3 minutes wash).

[0157] The product penetrates under hair via applicator connected to foam container, as shown in the picture below.

[0158] The foam was spread onto hair through gentle rubbing in. The product remained in contact with hair for 10 minutes and then was washed off with water and a usual shampoo. Treatment was repeated in 10 days.

[0159] In order to measure the applied amount of product, the foam container was weighed before and after every use.

## Results and Conclusions

[0160] 1. Efficacy:

[0161] The product is found effective in lice killing in 96.4% of the patients.

[0162] The product further eradicated viable nits in 60% of the patients.

[0163] 2. Safety:

[0164] No drug-related adverse effects were recorded.

[0165] 3. Usability:

[0166] A. Ease of Application.

[0167] Due to the nature a foam product, Foamix Permethrin 1% Foam was found easier to use in comparison with other products available in the market.

[0168] When foam is released it expands in the hair and reaches every spot where lice can be found. This advan-

tage is particularly meaningful in regards to such difficulty to access areas as in the neck and behind the ears.

[0169] Using the product with applicator attached to foam container directly onto the scalp under the hair is very convenient.

[0170] B. The Foam is Drip-Free

[0171] The foam is not liquid and therefore is not leaking when applied.

[0172] This allows precise application, without the product being spread on clothes or other parts of the body.

[0173] Not a single case of contact with eyes was recorded throughout the study. (It should be noted that the issue of contact with eyes is a common problem when treating with shampoo, lotion and spray which usually cause eye irritation and burning.)

[0174] C. Patients' response

[0175] Throughout the study it was evident that children enjoy being treated with foam and therefore do not resist the therapy.

[0176] In conclusion, the present study provides evidence that Foam H of Example 4 is safe and effective in the treatment of head lice (pediculosis capitis) in pediatric patients.

#### EXAMPLE 9

[0177] This example describes a single-blind study of the transepidermal water loss effect of PER 079 and PER 091 vehicle formulations from Example 6 in subjects with normal skin in comparison with Petrolatum and No Treatment.

[0178] Transepidermal water loss (TEWL) is often used to assess the occlusive effect of a composition. A single-blind study was carried out to assess the effect of two principal vehicle formulations on TEWL, in comparison with petrolatum (positive control) and no treatment (negative control). Square areas of the same size, 4 cm<sup>2</sup> each were drawn in the forearms. The areas were randomly assigned to a single treatment with one of the preparations (PER 079, PER 091 or petrolatum) and one area remained untreated. 40 mg of each of the preparations were applied. The following table provides the TEWL values prior to treatment (baseline) and 30 minutes afterwards.

	PER 079		PER 091		Petrolatum		No Treatment	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Baseline	3.8	0.4	3.8	0.5	3.8	0.5	4.1	0.5
30 min	3.4	0.3	3.6	0.3	1.7	0.2	3.8	0.4
% Change	-10.5%		-5.3%		-54.3%		-7.3%	

[0179] The following conclusions had been recorded in light of the study results:

[0180] 1. The positive control showed a significant decreased of 54.3% in the TEWL values 30 minutes after application, thus confirming that the experimental system responds to a positive control.

[0181] 2. The negative control (no-treatment) remains stable with negligible decrease of 7.3% after 30 minutes.

[0182] 3. Formulations PER 079 and PER 091 showed a similar pattern of TEWL change 30 minutes after treatment, with no significant difference between formulations. There was no significant difference in the TEWL change between formulations PER 079 and PER 091 and the negative control.

[0183] Hence, it could be concluded that formulations PER 079 and PER 091 are non-occlusive.

1. (canceled)

2. A composition comprising a carrier composition and a propellant, the carrier comprising:

i. an active agent;

ii. at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an organic polar solvent, an emollient, and mixtures of any two or more thereof, at a concentration of about 2% to about 50% by weight of the carrier composition;

iii. a foam adjuvant and a polymeric agent; and

iv. water;

wherein the propellant is a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the carrier composition; and wherein the polymeric agent is selected from the group consisting of bioadhesive agents, gelling agents, film forming agents, phase change agents, and mixtures of any two or more thereof.

3. The composition of claim 2, wherein the active agent is an insecticide.

4. The composition of claim 2, wherein the organic carrier is present at about 5% to about 50% by weight of the carrier composition and the foam adjuvant is present at about 0.1% to about 5% by weight of the carrier composition.

5. The composition of claim 2, wherein the carrier composition is an emulsion.

6. The composition of claim 2, further including about 0.1% to about 5% by weight of the carrier composition of a surface active agent.

7. The composition of claim 3, wherein the insecticide is selected from the group consisting of an antibiotic insecticide, a botanical insecticide, a carbamate insecticide, a dinitrophenol insecticide, a fluorine insecticide, an insect growth regulator, a chitin synthesis inhibitor, a juvenile hormone mimics, a moulting hormone agonist, a moulting inhibitor, a nereistoxin analogue insecticide, a nicotinoid insecticide, a pyridylmethylaniline insecticide, an organochlorine insecticide, a cyclodiene insecticide, an organophosphorus insecticide, an organophosphate insecticide, an organothiophosphate insecticides, an aliphatic amide organothiophosphate insecticide, an oxime organothiophosphate insecticide, a heterocyclic organothiophosphate insecticide, a benzothioiopyran organothiophosphate insecticide, a benzotriazine organothiophosphate insecticide, an isoindole organothiophosphate insecticide, an isoxazole organothiophosphate insecticide, a pyrazolopyrimidine organothiophosphate insecticide, a pyridine organothiophosphate insecticide, a pyrimidine organothiophosphate insecticide, a quinoxaline organothiophosphate insecticide, a thiadiazole organothiophosphate insecticide, a triazole organothiophosphate insecticide, a phenyl organothiophosphate insecticides, a phosphonothioate insecticide, a phenyl ethylphosphonothioate insecticide, a phenyl phenylphosphonothioate insecticide, a phosphoramidate insecticide, a phosphoramidothioate insecticide, a phosphorodiamide insecticide, an oxadiazine insecticide, a phthalimide insecticide, a pyrazole insecticide, a pyrethroid insecticide, a pyrethroid ester insecticide, a pyrethroid ether insecticide, a pyrimidinamine insecticide, a pyrrole insecticide, a tetrone acid insecticide, a thiourea insecticide, a urea insecticide, and mixtures of any two or more thereof.

8. The composition of claim 2, wherein the at least one active agent is selected from the group consisting of a steroidal antiinflammatory agent, an immunosuppressive agent, an immunomodulator, an immunoregulating agent, a hormonal

agent, an antibiotic agent, an antifungal agent, an antiviral agent, an antiparasitic agent, vitamin A, a vitamin A derivative, vitamin B, a vitamin B derivative, vitamin C, a vitamin C derivative, vitamin D, a vitamin D derivative, vitamin E, a vitamin E derivative, vitamin F, a vitamin F derivative, vitamin K, a vitamin K derivative, a wound healing agent, a disinfectant, an anesthetic, an antiallergic agent, an alpha hydroxyl acid, lactic acid, glycolic acid, a beta-hydroxy acid, a protein, a peptide, a neuropeptide, an allergen, an immunogenic substance, a haptene, an oxidizing agent, an antioxidant, a dicarboxylic acid, azelaic acid, sebacic acid, adipic acid, fumaric acid, a retinoid, an antiproliferative agent, an anticancer agent, a photodynamic therapy agent, benzoyl chloride, calcium hypochlorite, magnesium hypochlorite, an anti-wrinkle agent, a radical scavenger, a metal, silver, a metal oxide, titanium dioxide, zinc oxide, zirconium oxide, iron oxide, silicone oxide, talc, carbon, an anti wrinkle agent, a skin whitening agent, a skin protective agent, a masking agent, an anti-wart agent, a refatting agent, a lubricating agent, and mixtures of any two or more thereof.

9. The composition of claim 2, wherein the organic carrier comprises a potent solvent selected from the group consisting of propylene glycol, hexylene glycol, benzyl alcohol, terpene-ol, dimethyl isosorbide, a polyol, butanediol, diethylene glycol, terpenes, di-terpenes, tri-terpenes, limonene, dioxolane, dimethylformamide, dimethyl sulfoxide, methyl dodecyl sulfoxide, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, isosorbide derivatives, glycofurol, ethoxydiglycol, and mixtures of any two or more thereof.

10. The composition of claim 6, wherein the surface active agent is non-ionic or a combination of non-ionic and ionic surface active agents, wherein the ratio of non-ionic surface active agent to ionic surface active agent is about 6:1 or greater than 6:1.

11. The composition of claim 6, wherein the organic carrier is a hydrophobic solvent and wherein the surface active agent is present at a concentration of about 0.1% to about 5% by weight of the carrier composition.

12. The composition of claim 2, wherein the organic carrier is an organic polar solvent.

13. The composition of claim 2, wherein the foam adjuvant is selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain, a fatty acid having 16 or more carbons in their carbon chain, fatty alcohols derived from beeswax, a fatty alcohol having at least one double bond, a fatty acid having at least one double bond, a branched fatty alcohol, a branched fatty acid, a fatty acid substituted with a hydroxyl group, cetyl alcohol, stearyl alco-

hol, arachidyl alcohol, behenyl alcohol, 1-triacontanol, hexadecanoic acid, stearic acid, arachidic acid, behenic acid, octacosanoic acid, 12-hydroxy stearic acid, and mixtures of any two or more thereof.

14. The composition of claim 2, wherein the at least one polymeric agent selected from the group consisting of naturally-occurring polymeric materials, a locust bean gum, sodium alginate, sodium caseinate, an egg albumin, a gelatin agar, a carrageenin gum, an xanthan gum, a quince seed extract, a tragacanth gum, a guar gum, a starch, chemically modified starches, semi-synthetic polymeric materials, cellulose ethers, a hydroxyethyl cellulose, a hydroxypropyl cellulose, a methyl cellulose, a carboxymethyl cellulose, a methylhydroxyethylcellulose, hydroxypropyl methylcellulose, a hydroxyethyl carboxymethylcellulose, a carboxymethylcellulose, a hydroxypropyl guar gum, a soluble starch, cationic celluloses, cationic guar, synthetic polymeric materials, carboxyvinyl polymers, a polyvinylpyrrolidone, a polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers, acrylic acid/ethyl acrylate copolymers, carboxyvinyl polymers, a colloidal water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with polyallyl sucrose or polyallyl pentaerythritol, carbomer 934, carbomer 940, carbomer 950, carbomer 980, carbomer 951, carbomer 981, silicon dioxide, a poloxamer, and mixtures of any two or more thereof.

15. The composition of claim 2, wherein the active agent is selected from the group consisting of niacinamide, tazarotene, azelaic acid, permethrin, and mixtures of any two or more thereof.

16. The composition of claim 4, wherein the at least one organic carrier is selected from the group consisting of caprylic/capric triglyceride, isopropyl myristate, cyclomethicone, dimethicone, castor oil, oleyl alcohol, diisopropyl adipate, mineral oil, and mixtures of any two or more thereof.

17. The composition of claim 2, further comprising an excipient selected from the group consisting of a stabilizing agent, an antioxidant, a humectant, a preservative, a colorant, an odorant, and mixtures of any two or more thereof.

18. The composition of claim 3, wherein the insecticide is capable of treating or alleviating a disorder involving an anthropod or parasite.

19. The composition of claim 2, wherein the active agent is water soluble, oil soluble, or both.

20. The composition of claim 2, wherein the carrier composition does not form an impermeable occlusive barrier.

21. The composition of claim 2, wherein the carrier composition comprises less than 5% or about 5% by weight of lower alcohols.

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