Claims

1. Use of a nanoemulsion comprising a population of particles, wherein the majority of particles have diameters between 10 and 300 nanometers, and wherein the nanoemulsion comprises an oil, a surfactant and at least one therapeutic agent, wherein the oil and surfactant are present in a ratio ranging from 0.5-2.0;

in the manufacture of a medicament for the treatment of disorders associated with the dermal level of the skin, wherein the disorder associated with the dermal level of the skin is selected from the group consisting of: bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis, excess sebum-producing disorders, Raynaud's phenomenon, lupus erthythematous, hyperpigmentation disorder, hypopigmentation disorder, and skin cancer.

2. The use according to claim 1, wherein the therapeutic agent is a polypeptide, nucleic acid, a lipid, a carbohydrate, a small molecule, an antibiotic, an antibody, benzoyl peroxide, isotretinoin, or azelaic acid, or wherein the therapeutic agent is selected from the group consisting of a topical bactericidal, benzoyl peroxide, triclosan, chlorhexidine gluconate, an oral antibiotic, a topical antibiotic, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotics, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, Stiemycin, mupirocin, a hormone, cortisone, a topical retinoid, tretinoin, adapalene, tazarotene, retinol, a natural product with anti-acne activity, aloe vera, aruna, haldi, papaya, tea tree oil, azelaic acid, nicotinamide, an antiperspirant, aluminium chloride, aluminium chlorohydrate, aluminium-zirconium compounds, aluminium zirconium tetrachlorohydrex gly, aluminium zirconium trichlorohydrex gly, ammonium alum, oral isotretinoin, topical sulfacetamide, topical sulfur, topical calcineurin inhibitor, tacrolimus, pimecrolimus, topical permethrin, a combination of plant-sourced Methylsulfonylmethane (MSM) and Silymarin, an aza-steroid, finasteride, dutasteride, minoxidil, an antiandrogen, ketoconazole, fluconazole, spironolactone, saw palmetto, caffeine, copper peptides, nitroxide spin labels TEMPO and TEMPOL, unsaturated fatty acids, gamma linolenic acid, hedgehog agonists, azelaic acid and zinc in combination, Chinese knotweed, pumpkin seed, zinc, stinging nettle, coal tar, dithranol, a corticosteroid, desoximetasone, a vitamin D3 analog, calcipotriol, argan oil, topical psoralen with exposure to ultraviolet A (UVA) light, milk thistle, methotrexate, cyclosporine, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, pimecrolimus, alefacept, etanercept, infliximab, rituximab, efalizumab, adalimumab, ustekinumab, topical mixture of bacitracin and polymyxin, topical fusidic acid cream, antiviral therapeutics, acyclovir,

famciclovir, valacyclovir, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod, terbinafine, clotrimazole, econazole, selenium sulfide shampoo, ketoconazole shampoo, itraconazole, 5-fluorouricil, imiquimod, diclofenac, crocodile oil, and combinations thereof.

3. The use according to any one of the preceding claims, wherein the oil and surfactant are present in the ratio ranging from 0.5-1.0.

4. The use according to any one of the preceding claims, wherein the nanoemulsion is to be administered to the patient's skin without significant unwanted side effects.

5. The use according to claim 4, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by 50%, 60%, 70%, 80%, 90%, or 95% relative to injection or oral administration of the same therapeutic agent.

6. The use according to claims 4 or 5, wherein the unwanted side effect is selected from the group consisting of bruising, hematoma, pain, ecchymosis, unwanted systemic effects, undesirable blood levels, botulism, damage to underlying nervous tissue, neuronal paralysis, unwanted effects on muscles, muscle paralysis, and flu-like symptoms.

7. The use according to any one of the preceding claims, wherein the majority of particles have a range of diameters between 10 and 200 nanometers, 10 and 150 nanometers, 10 and 120 nanometers, 10 and 100 nanometers, or 10 and 50 nanometers.

8. The use according to any one of the preceding claims, wherein the population of particles is substantially free of particles having a diameter in excess of 300 nm, 200 nm, or 120 nm.

9. The use according to any of the preceding claims, wherein fewer than 50%, 25%, 10%, 5% or 1% of the particles have a diameter in excess of 300 nm, 200 nm, or 120 nm.

10. The use according to any one of the preceding claims, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed 600 nm, 300 nm, 100 nm, or 50 nm.

~~11. The use according to any one of the preceding claims, wherein the particles have an average diameter of 100 nm, 75 nm, or wherein the particles have an average diameter ranging between 100-300 nm, 50-250 nm, 70-130 nm, 10-100 nm, 50-100 nm.~~

~~12. The use according to any one of the preceding claims, wherein the nanoemulsion is substantially free of toxic solvents or the nanoemulsion comprises less than 50%, 25%, 10%, 5% or 1% of toxic solvents.~~

~~13. The use according to any one of the preceding claims, wherein the nanoemulsion is stable or wherein the majority of particles are stable for at least 1 day, at least 2 months, at least 5 months, at least 12 months, at least 24 months.~~

~~14. The use according to any one of the preceding claims, wherein the nanoemulsion was generated by exposure to high shear force, by microfluidization, by cavitation or by high pressure homogenization optionally wherein the microfluidization is single-pass microfluidization.~~

~~15. The use according to any one of the preceding claims, wherein the nanoemulsion was generated by exposure to high shear force for less than 10 minutes, for less than 2 minutes, for less than 1 minute, or for less than 30 seconds, or wherein the nanoemulsion was generated by exposure to pressures greater than 3,000 psi, greater than 10,000 psi, greater than 18,000 psi, greater than 24,000 psi, greater than 30,000 psi, greater than 40,000 psi or wherein the nanoemulsion was generated by microfluidization at a pressure greater than 3,000 psi, greater than 10,000 psi, greater than 18,000 psi, greater than 21,000 psi, greater than 24,000 psi, greater than 30,000 psi, or greater than 40,000 psi.~~

Claims

~~16~~1. Use of a nanoemulsion comprising a population of particles, wherein the majority of particles have diameters between 10 and 300 nanometers, and wherein the nanoemulsion comprises an oil, a surfactant and at least one therapeutic agent, wherein the oil and surfactant are present in a ratio ranging from 0.5-2.0;

in the manufacture of a medicament for the treatment of disorders associated with the dermal level of the skin, wherein the disorder associated with the dermal level of the skin is selected from the group consisting of: bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis, excess sebum-producing

disorders, Raynaud's phenomenon, lupus erthythematous, hyperpigmentation disorder, hypopigmentation disorder, and skin cancer;

and wherein the therapeutic agent is botulinum toxin optionally wherein the botulinum toxin is

(a) encapsulated within the particles;
(b) adsorbed on the surface of the particles;
(c) associated with the particle interface;
(d) Selected from the group comprising type A, type B, type C1, type C2, type D, type E, type F and type G;
(e) a botulinum complex;
(f) incorporated within an albumin matrix;
(g) not incorporated within an albumin matrix;
(h) a purified botulinum toxin protein or fragment thereof;
(i) isolated, or substantially isolated, from other proteins;
(j) isolated, or substantially isolated, from non-toxin proteins;
(k) chemically synthesized;
(l) produced recombinantly;
(m) a fragment of a wild-type toxin; or
(n) contains at least one mutation relative to the wild-type toxin.

~~17~~2. The use according to ~~any of the previous claims~~claim 1, wherein the nanoemulsion can penetrate skin without altering or changing the skin, or without the use of skin or chemical or mechanical permeation enhancers or abrasives.

~~18~~3. The use according to any of the previous claims, wherein the nanoemulsion can penetrate the top layer of skin without the use of skin permeation enhancers or abrasives optionally wherein the top layer of the skin is the surface of the stratum corneum, or wherein the top layer of the skin includes dermal pores, or dermal glands.

~~19~~4. The use according to any of the preceding claims, wherein the oil is selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl

myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ, and 1349 oils, and combinations thereof, or is a medium-chain triglyceride, or is selected from the group consisting of butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof, or wherein the surfactant is a non-ionic detergent, or is selected from the group consisting of phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (Span 85) glycocholate; sorbitan monolaurate (Span 20); polysorbate 20 (TWEEN®20); polysorbate 60 (TWEEN®60); polysorbate 65 (TWEEN®65); polysorbate 80 (TWEEN®80); polysorbate 85 (TWEEN®85); super- refined polysorbate 20 (SR TWEEN®20); super-refined polysorbate 60 (SR TWEEN®60); super-refined polysorbate 65 (SR TWEEN®65); super-refined polysorbate 80 (SR TWEEN®80); super-refined polysorbate 85 (SR TWEEN®85); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebrosides; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000- phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; and combinations thereof.

~~205~~. The use according to any of the preceding claims, wherein the nanoemulsion does not have more than one oil or more than one surfactant.

~~216~~. The use according to any of the preceding claims, wherein the oil and surfactant are present in a ratio ranging from 1.5-2.0.

~~227~~. The use according to any of the preceding claims, wherein the percent of oil in the nanoemulsion ranges from 1% - 10%, 7%, 6%, 5% or wherein the percent of surfactant in the nanoemulsion ranges from 1% - 20%, 1% - 10%, or 9% or 10%.

~~238~~. The use according to any of the previous claims, wherein the nanoemulsion is provided as a pharmaceutical composition comprising the nanoemulsion and at least one pharmaceutically acceptable excipient, optionally wherein the composition is selected from the group consisting of a cream, a lotion, a liniment, a gel, an ointment, a spray, a powder, an emollient, an aerosol, and combinations thereof or wherein the composition is to be administered transdermally using adhesive patch or a deodorant stick.

~~249~~. The use according to any of the previous claims, wherein the therapeutic agent permeates the skin or wherein at least 99%, at least 95%, at least 90%, at least 75%, at least 50%, at least 25%, at least 10% or at least 1% of the therapeutic agent permeates the skin.

~~25. Use of a nanoemulsion comprising a population of particles, wherein the majority of particles have diameters between 10 and 300 nanometers, and wherein the nanoemulsion comprises an oil, a surfactant and at least one therapeutic agent, wherein the oil and surfactant are present in a ratio ranging from 0.5-2.0;~~

~~wherein the nanoemulsion does not contain botulinum toxin;~~

~~in the manufacture of a medicament for the treatment of disorders associated with the dermal level of the skin, wherein the disorder associated with the dermal level of the skin is selected from the group consisting of: bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis, excess sebum-producing disorders, Raynaud's phenomenon, lupus erythematous, hyperpigmentation disorder, hypopigmentation disorder, and skin cancer;~~

~~and wherein the therapeutic agent is a polypeptide, nucleic acid, a lipid, a carbohydrate, a small molecule, an antibiotic, an antibody, benzoyl peroxide, isotretinoin, or azelaic acid, or wherein the therapeutic agent is selected from the group consisting of a topical bactericidal, benzoyl peroxide, triclosan, chlorhexidine gluconate, an oral antibiotic, a topical antibiotic, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotics, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, Stiemycin, mupirocin, a hormone, cortisone, a topical~~

~~retinoid, tretinoin, adapalene, tazarotene, retinol, a natural product with anti-acne activity, aloe vera, aruna, haldi, papaya, tea tree oil, azelaic acid, nicotinamide, an antiperspirant, aluminium chloride, aluminium chlorohydrate, aluminium-zirconium compounds, aluminium zirconium tetrachlorohydrex gly, aluminium zirconium trichlorohydrex gly, ammonium alum, oral isotretinoin, topical sulfacetamide, topical sulfur, topical calcineurin inhibitor, tacrolimus, pimecrolimus, topical permethrin, a combination of plant-sourced Methylsulfonylmethane (MSM) and Silymarin, an aza-steroid, finasteride, dutasteride, minoxidil, an antiandrogen, ketoconazole, fluconazole, spironolactone, saw palmetto, caffeine, copper peptides, nitroxide spin labels TEMPO and TEMPOL, unsaturated fatty acids, gamma linolenic acid, hedgehog agonists, azelaic acid and zinc in combination, Chinese knotweed, pumpkin seed, zinc, stinging nettle, coal tar, dithranol, a corticosteroid, desoximetasone, a vitamin D3 analog, calcipotriol, argan oil, topical psoralen with exposure to ultraviolet A (UVA) light, milk thistle, methotrexate, cyclosporine, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, pimecrolimus, alefacept, etanercept, infliximab, rituximab, efalizumab, adalimumab, ustekinumab, topical mixture of bacitracin and polymyxin, topical fusidic acid cream, antiviral therapeutics, acyclovir, famciclovir, valacyclovir, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod, terbinafine, clotrimazole, econazole, selenium sulfide shampoo, ketoconazole shampoo, itraconazole, 5-fluorouricil, imiquimod, diclofenac, crocodile oil, and combinations thereof.~~

~~26. The use according to claim 25, wherein the oil and surfactant are present in the ratio ranging from 0.5-1.0.~~

10. The use according to any one of the preceding claims, wherein the nanoemulsion is to be administered to the patient's skin without significant unwanted side effects.

11. The use according to claim 10, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by 50%, 60%, 70%, 80%, 90%, or 95% relative to injection or oral administration of the same therapeutic agent; wherein the unwanted side effect is pain, bruising, ecchymosis, or hematoma.

12. The use according to claims 10 or 11, wherein the unwanted side effect is selected from the group consisting of bruising, hematoma, pain, ecchymosis, unwanted systemic effects, undesirable blood levels, botulism, damage to underlying nervous tissue, neuronal paralysis, unwanted effects on muscles, muscle paralysis, and flu-like symptoms.

13. The use according to any one of the preceding claims, wherein the majority of particles have a range of diameters between 10 and 200 nanometers, 10 and 150 nanometers, 10 and 120 nanometers, 10 and 100 nanometers, or 10 and 50 nanometers.

14. The use according to any one of the preceding claims, wherein the population of particles is substantially free of particles having a diameter in excess of 300 nm, 200 nm, or 120 nm.

15. The use according to any of the preceding claims, wherein fewer than 50%, 25%, 10%, 5% or 1% of the particles have a diameter in excess of 300 nm, 200 nm, or 120 nm.

16. The use according to any one of the preceding claims, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed 300 nm, 100 nm, or 50 nm.

17. The use according to any one of the preceding claims, wherein the particles have an average diameter of 100 nm, 75 nm, or wherein the particles have an average diameter ranging between 100-300 nm, 50-250 nm, 70-130 nm, 10-100 nm, 50-100 nm.

18. The use according to any one of the preceding claims, wherein the nanoemulsion is substantially free of toxic solvents or the nanoemulsion comprises less than 50%, 25%, 10%, 5% or 1% of toxic solvents, wherein the toxic solvents are dimethyl sulfoxide, dimethyl acetimide, dimethyl formamide, chloroform, tetramethyl formamide, acetone, acetates, or alkanes.

19. The use according to any one of the preceding claims, wherein the nanoemulsion is stable; or wherein the average particle size, the maximum particle size, the range of particle sizes, or the distribution of particle sizes is maintained for at least 1 day, at least 2 months, at least 5 months, at least 12 months, at least 24 months.

20. The use according to any one of the preceding claims, wherein the nanoemulsion was generated by exposure to high shear force, by microfluidization, by cavitation or by high pressure homogenization optionally wherein the microfluidization is single-pass microfluidization.

21. The use according to any one of the preceding claims, wherein the nanoemulsion was generated by exposure to high shear force for less than 10 minutes, for less than 2 minutes, for less than 1 minute, or for less than 30 seconds, or wherein the nanoemulsion was generated by exposure to pressures greater than 3,000 psi, greater than 10,000 psi, greater than 18,000 psi, greater than 24,000 psi, greater than 30,000

psi, greater than 40,000 psi or wherein the nanoemulsion was generated by microfluidization at a pressure greater than 3,000 psi, greater than 10,000 psi, greater than 18,000 psi, greater than 21,000 psi, greater than 24,000 psi, greater than 30,000 psi, or greater than 40,000 psi.