Patent No. 5,993,852 describes biphasic lipid vesicle compositions for transdermal administration of an immunogen.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a biphasic lipid vesicle composition comprising:

a) one or more lipid vesicles comprising a lipid bilayer comprising vesicle forming lipids,

b) an oil-in-water emulsion entrapped in the biphasic lipid vesicles; and

c) one or more penetration enhancing agents entrapped in the lipid bilayer or the oil-in-water emulsion;

wherein the one or more penetration enhancing agents comprise one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 or less.

[0006] The present disclosure includes a biphasic lipid vesicle composition comprising:

a) lipid vesicles each comprising a lipid bilayer comprising vesicle forming lipids,

b) an oil-in-water emulsion entrapped in the biphasic lipid vesicles, and stabilized by one or more surfactants;

c) one or more compounds entrapped in the lipid bilayer and/or the oil-in-water emulsion;

d) one or more penetration enhancing agents entrapped in the lipid bilayer and/or the oil-in-water emulsion;

wherein the one or more penetration enhancing agents are one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 or less.

[0007] The present application also includes a biphasic lipid vesicle composition comprising:

a) lipid vesicles comprising a lipid bilayer comprising vesicle forming lipids,

b) an oil-in-water emulsion entrapped in the biphasic lipid vesicles, and comprising one or more polycationic surfactants; and

c) one or more compounds entrapped in the lipid bilayer and/or the oil-in-water emulsion.

[0008] The present application also further includes method of preparing biphasic lipid vesicles of the disclosure comprising:

a) preparing an oil-in-water emulsion comprising one or more surfactants, by mixing oil components of the oil-in-water emulsion with aqueous components of the oil-in-water emulsion, wherein the oil components and/or the aqueous components of the oil-in-water emulsion comprises the one or more surfactants;

b) solubilizing vesicle forming lipids in an acceptable solvent other than water;

c) adding one or more compounds and one or more penetration enhancing agents to the oil components and/or the aqueous components of step a), and/or the solubilized vesicle forming lipids of step b);

CLAIMS

1. A biphasic lipid vesicle composition comprising:

a) one or more lipid vesicles ~~each~~ comprising a lipid bilayer comprising vesicle forming lipids,

b) an oil-in-water emulsion entrapped in the biphasic lipid vesicles~~, and stabilized by one or more surfactants~~; and

~~c) one or more compounds entrapped in the lipid bilayer and/or the oil-in-water emulsion;~~

~~d~~c) one or more penetration enhancing agents entrapped in the lipid bilayer ~~and/~~or the oil-in-water emulsion;

wherein the one or more penetration enhancing agents comprise~~are~~ one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 or less.

~~2. The biphasic lipid vesicle composition of claim 1, wherein the biphasic lipid vesicle composition is a cosmetic composition.~~

~~3. The biphasic lipid vesicle composition of claim 1, wherein the biphasic lipid vesicle composition is a pharmaceutical composition.~~

~~4. The biphasic lipid vesicle composition of any one of claim 1 to 3, wherein the biphasic lipid vesicle composition is for topical delivery of the one or more compounds.~~

~~5. The biphasic lipid vesicle composition of any one of claim 1 to 4, wherein the biphasic lipid vesicle composition comprises a suspension of the biphasic lipid vesicles.~~

~~6~~2. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim 1 ~~to 5~~, wherein the one or more penetration enhancing agents are entrapped in the oil-in-water emulsion ~~of the biphasic lipid vesicle~~.

~~7. The biphasic lipid vesicle composition of claim 6, wherein the oil-in-water emulsion comprises about 0.5 wt % to about 9 wt %, about 0.5 wt % to about 8 wt %, about 0.5 wt % to about 7 wt %, about 1 wt % to about 6 wt %, about 1 wt % to about 5 wt %, about 1 wt % to about 4 wt %, about 1 wt % to about 3 wt %, or about 1 wt % to about 2 wt % of the one or more penetration enhancing agents.~~

~~8~~3. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim 1 ~~to 5~~, wherein the one or more penetration enhancing agents are entrapped in the lipid bilayer and the oil-in-water emulsion.

~~9~~4. The ~~biphasic lipid vesicle~~ composition of claim 1~~8~~, wherein the lipid bilayer comprises about 10 wt %, about 9 wt %, about 8 wt %, about 7 wt %, about 6 wt %, about 5 wt %, about 4 wt %, about 3 wt %, about 2 wt %~~-~~, about 1 wt %, about 0.5 wt % or about 0.1 wt % ~~-~~of the one or more ~~skin~~ penetration enhancing agents.

~~10. The biphasic lipid vesicle composition of any one of claim 1 to 5, wherein the one or more penetration enhancing agents are entrapped in both the lipid bilayer and the oil-in-water emulsion of the biphasic lipid vesicle.~~

~~11~~5. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim 1 ~~to 10~~, wherein the ~~one or more penetration enhancing agents are~~ one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 or less are selected from one or more of polyethylene glycol ethers of fatty alcohols, sorbitan esters, polysorbates, ~~sorbitan esters and~~ polyethylene glycol fatty acid esters, or any combination ~~and combinations~~ thereof.

~~12~~6. The ~~biphasic lipid vesicle~~ composition of claim 5~~11~~, wherein the polyethylene glycol ethers of fatty alcohols are selected from ~~Ceteth-2®(Diethylene~~ diethylene glycol hexadecyl ether~~)~~, ~~Steareth-2®(~~2-(2-octadecoxyethoxy)ethanol~~)~~, ~~Oleth-2®(~~diethylene glycol monooleyl ether~~)~~, ~~Oleth-3®(~~ ~~P~~polyoxyethylene (3) ~~O~~oleyl ~~E~~ether~~)~~, ~~and Oleth-5®(P~~polyoxyethylene (5) ~~O~~oleyl ~~E~~ether~~)~~, ~~-~~or any~~and~~ combination~~s~~ thereof.

~~13. The biphasic lipid vesicle composition of claim 12, wherein the polyethylene glycol ethers is Oleth-2® (diethylene glycol monooleyl ether).~~

~~14~~7. The ~~biphasic lipid vesicle~~ composition of claim ~~13~~5, wherein the polyethylene glycol fatty acid esters are selected from ~~one or more or more~~ PEG-8 dilaurate, PEG-4 dilaurate, PEG-4 laurate, PEG-8 dioleate, PEG-8 distearate, PEG-8 distearate, PEG-7 glyceryl cocoate, ~~and~~ PEG-20 almond glycerides, or any combination ~~and combinations~~ thereof.

~~15. The biphasic lipid vesicle composition of claim 14, wherein the polyethylene glycol fatty acid esters is PEG-4 dilaurate.~~

~~16~~8. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim 1 ~~to 11~~, wherein the one or more penetration enhancing agents further comprise~~are one or more non-ionic surfactants having a HLB of about 10 or less in combination with one or more penetration enhancing agents selected from one or more~~ terpenes, alkaloids, salicylate derivatives, ~~and~~ polycationic surfactants, or any combination ~~and combinations~~ thereof.

~~17. The biphasic lipid vesicle composition of claim 16, wherein the one or more penetration enhancing agents are one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 are the one or more penetration enhancing agents are one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of about 10 of any one of claims 11 to 15.~~

~~18~~9. The ~~biphasic lipid vesicle~~ composition of claim ~~8~~16 ~~or claim 17~~, wherein the ~~one or more~~ terpenes are selected from one or more of eugenol, d-limonene, menthol, menthone, farnesol, neridol, camphor, nerol~~,~~ ~~and~~ thymol, or any combination~~and combinations~~ thereof.

~~19. The biphasic lipid vesicle composition of claim 18, wherein the one or more terpenes are selected from one or more of menthol, camphor, nerol and thymol, and combinations thereof.~~

~~20~~10. The ~~biphasic lipid vesicle~~ composition of claim ~~8~~16 ~~or claim 17~~, wherein the ~~one or more~~ salicylate derivatives ~~is~~ are selected from one or more of ethyl salicylate, salicylic acid, acetylsalicylic acid~~,~~ ~~and~~ trolamine salicylate, or any~~and~~ combination~~s~~ thereof.

~~21. The biphasic lipid vesicle composition of claim 20, wherein the salicylate derivative is methyl salicylate.~~

~~22~~11. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ ~~8~~16 ~~to 21~~, wherein the ~~one or more~~ alkaloids are selected from piperine, lobeline, caffeine, theobromine theophylline, nicotine, colchicine, N-methyl pyrrolidone, hygrine, capsaicin, berberine, sanguinarine, histamine~~,~~ ~~and/or~~ pilocarpine, or any combination thereof.

~~23. The biphasic lipid vesicle composition of claim 22, wherein the one or more alkaloids is piperine.~~

~~24~~12. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ ~~8~~16 ~~to 23~~, wherein the polycationic surfactants comprise~~are~~ one or more gemini cationic surfactants and the one or more gemini cationic surfactants are of a quaternary ammonium type.

~~25~~13. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ ~~8~~16 ~~to 22~~, wherein the polycationic surfactants comprise~~are~~ polycationic amino acids.

~~26. The biphasic lipid vesicle composition of any one of claim 1 to 25 wherein the penetration enhancing agents are one or more non-ionic surfactants having a HLB of about 9 or less, about 8 or less, about 7 or less, or about 6 or less and optionally having a HLB of 1 or more, 2 or more, 3 or more or 4 or more or any combination thereof.~~

~~27. The biphasic lipid vesicle composition of any one of claim 1 to 12, wherein the penetration enhancing agent is Oleth-2®.~~

~~28. The biphasic lipid vesicle composition of claim 16, wherein the penetration enhancing agents are Oleth-2® in combination with one or more of menthol, camphor, nerol or thymol, or combinations thereof.~~

~~29. The biphasic lipid vesicle composition of claim 16, wherein the penetration enhancing agents are Oleth-2® in combination with methyl salicylate~~

~~30. The biphasic lipid vesicle composition of claim 16, wherein the penetration enhancing agents are Oleth-2® in combination with piperidine.~~

~~31. The biphasic lipid vesicle composition of claim 30, wherein one or more non-ionic surfactants having a HLB of about 10 or less is entrapped in the lipid bilayer, and the one or more terpenes or the one or more alkaloids are entrapped in the lipid bilayer, the oil-in-water emulsion or both.~~

~~32. The biphasic lipid vesicle composition of any one of claims 1 to 11, wherein the one or more penetration enhancing agent is PEG-4 dilaurate.~~

~~33. The biphasic lipid vesicle composition of claim 16, wherein the one or more penetration enhancing agents are PEG-4 dilaurate in combination with piperidine.~~

~~34. The biphasic lipid vesicle composition of claim 16, wherein the one or more penetration enhancing agents are PEG-4 dilaurate in combination with methyl salicylate.~~

~~35~~14. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ 1~~ to 11~~, wherein the one or more penetration enhancing agents comprise diethylene glycol monooleyl ether~~are Oleth-2~~, PEG-4 dilaurate~~, or~~ sorbitan monopalmitate, or any combination~~s~~ thereof.

~~36~~15. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ 1~~ to 34~~, wherein the oil-in-water emulsion of the biphasic lipid vesicles is stabilized by one or more surfactants comprising ~~or more surfactants selected from Ceteth-10® (~~polyoxyethylene (10) cetyl ether~~)~~ and ~~Tween 80 (~~polysorbate 80.~~)~~

~~37~~16. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ 1~~ to 35~~, wherein the vesicle forming lipids are selected from one or more of phospholipids, glycolipids, lecithins, ~~and/~~or ceramides~~ such as phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, cardiolipin, phosphatidic acid, and/or cerebroside~~.

~~38. The biphasic lipid vesicle composition of claim 36, wherein the vesicle forming lipids are phospholipids.~~

~~39~~17. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ 1~~ to 37~~, ~~wherein the one or more~~further comprising one or more compounds ~~are~~ entrapped in the oil-in-water emulsion of the biphasic lipid vesicle, lipid bilayer of the biphasic lipid vesicle or both the oil-in-water emulsion and the lipid bilayer.

4018. The biphasic lipid vesicle composition of claimany one of claims 1, to 38 wherein, the one or more compounds comprise a are selected from small molecule, protein, peptide, carbohydratemolecules, proteins, peptides, carbohydrates, nucleic acids, vaccine antigen,antigens, and/or plant extract, or any combination thereof.extracts.

41. The biphasic lipid vesicle composition of claim 36, wherein the small molecules prostaglandins, anesthetic agents such as ibuprofen and/or diclofenac; analgesics and/or sedatives including opioids such as buprenorphine, fentanyl, sufentanil, alfentanil and/or remifentanil; cardioactive medication such as organic nitrates including nitroglycerin, isosorbide dinitrate and/or isosorbide mononitrate, quinidine sulphate, procainamide, thiazides such as bendroflumethiazide, chlorothiazide and/or hydrochlorothiazide, nifedipine, nicardipine; adrenergic blockers such as timolol and/or propranolol, verapamil, diltiazem, captopril, clonidine or prazosine, androgenic steroids such as testosterone, methyltestosterone and/or fluoxymesterone; estrogens such as estradiol valerate, equilin, mestranol, estrone, estriol, 17.beta.-ethinylestradiol and/or diethylstilbestrol; progestogens such as are progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, chlormadinone, ethisterone, etonogestrel, medroxyprogesterone acetate, hydroxyprogesterone caproate, norethynodrel, norelgestromin, 17.alpha.-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone and/or megestrolacetate; antihistamines such as tihistamines are diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, clorprenaline, terfenadine and/or chlorpheniramine; antiviral agents, vitamins, anti-inflammatory agents such as acemetacin, acetamidocaproic acid, bendazac, benoxaprofen, bermoprofen, bucloxic acid, butibufen, cinmetacin, clidanac, clopirac, felbinac, fenbufen, fenclozic acid, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibuprofen, indomethacin, isofezolac, isoxepac, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, naproxen, oxaprozin, pirazolac, pirprofen, pranoprofen, protizinic acid, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, and/or tropesin. bermoprofen, bucloxic acid, isoxepac, ketoprofen, loxoprofen, zaltoprofen, ampiroxicam, bucolome, celecoxib, difenpiramide, mofebutazone, nimesulide, paranyline, parecoxib, parsalmide, piketoprofen, talniflumate, tenidap, terofenamate, valdecoxib, 21-acetoxypregnenolone, alclometasone, betamethasone, alfa-bisabolol, budesonide, clobetasone, cyclosporin, deflazacort, dexamethasone, diflorasone, desonide, desoximetasone, diflorasone, diflucortolone, difluprednate, ditazol, everolimus, fluazacort, fludrocortisone, flumethasone, fluocinolone, fluocinonide, fluocortin butyl, fluocortolone, fluprednidene acetate, glucametacin, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortisone, ibuproxam, loteprednol etabonate, mazipredone, memetasone, methylprednisolone, mometasone furoate, oxyphenbutazone, perisoxal, pimecrolimus, prednisolone, prednisone, rimexolone, sirolimus, triamcinolone and tacrolimus; antifungal agents, corticosteroids, vitamins, anti-infectives such as antibiotics, including penicillin, tetracycline, chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and/or sulfisoxazole; antiviral agents;

~~antibacterial agents such as erythromycin and/or clarithromycin, and/or other anti-infectives including nitrofurazone and the like; dermatological agents such as dermatological agents are vitamin A and/or vitamin E; medication for the treatment of nausea and sickness such as chlorpromazine, granisetron, perphenazine, prochlorperazine, promethazine, thiethylperazine, trifluprom azine and/or trimeprazine; amino acids, short peptides (upto 1000 Da), carbohydrates and/or natural compounds.~~

~~42~~19. The ~~biphasic lipid vesicle~~ composition of ~~any one of~~ claim~~s~~ 1 ~~to 41~~, wherein~~,~~ the biphasic lipid vesicle formulations ~~optionally~~ further comprise~~s~~ one or more other lipid vesicle components comprising a ~~including but limited to~~ fatty substance~~s~~, penetration enhancer~~s~~, surfactant~~s~~, ~~and/or~~ solvents, or any~~and~~ combination~~s~~ thereof.

~~43. A biphasic lipid vesicle composition comprising:~~

~~a) lipid vesicles comprising a lipid bilayer comprising vesicle forming lipids,~~

~~b) an oil-in-water emulsion entrapped in the biphasic lipid vesicles, and comprising one or more polycationic surfactants; and~~

~~c) one or more compounds entrapped in the lipid bilayer and/or the oil-in-water emulsion.~~

20. The composition of claim 1, wherein the one or more non-ionic surfactants is diethylene glycol monooleyl ether.

~~44. The biphasic lipid vesicle composition of claim 43, wherein the biphasic lipid vesicle composition is a cosmetic composition.~~

~~45. The biphasic lipid vesicle composition of claim 44, wherein the biphasic lipid vesicle composition is a pharmaceutical composition.~~

~~46. The biphasic lipid vesicle composition of any one of claim 43 to 45, wherein the biphasic lipid vesicle composition is for topical delivery of the one or more compounds.~~

~~47. The biphasic lipid vesicle composition of any one of claim 43 to 46, wherein the biphasic lipid vesicle composition comprises a suspension of the biphasic lipid vesicles.~~

~~48. The biphasic lipid vesicle composition of any one of claim 43 to 47, wherein one or more polycationic surfactants are one or more gemini cationic surfactants of a quaternary ammonium type.~~

~~49. The biphasic lipid vesicle composition of claim 48, wherein the one or more gemini cationic surfactants selected from the group consisting of 12-7NH-12, 12-7NCH_3-12, 16-3-16, 12-4$(OH)_2$-12, and 12-EO1-12.~~

~~50. The biphasic lipid vesicle composition of any one of claim 43 to 47, wherein one or more polycationic surfactants are polycationic amino acids.~~

~~51. The biphasic lipid vesicle composition of any one of claim 43 to 50, wherein the oil-in-water emulsion of the biphasic lipid vesicles comprises from about 0.01 to about 5%, 0.05 to about 5%, 0.1% to about 5%, about 1% to about 5%, or about 2% to about 5% of the one or more polycationic surfactants.~~

~~52. The biphasic lipid vesicle composition of any one of claim 43 to 51, wherein the one or more compounds are selected from small molecules including negatively charged small molecules, carbohydrates, nucleic acids such as RNA or DNA or hybrids thereof, plasmid DNA, oligonucleotides, including synthetic oligonucleotides, viral DNA, DNA vaccines, and the like, protein, peptides including peptide antigens such as vaccines antigens, immunoglobulins, immunomodulators, hormones, toxins, and/or enzymes, as well as plant extracts, and vitamins.~~

~~53. A method of preparing biphasic lipid vesicles of any one of claims 1 to 52 comprising:~~

~~a) preparing an oil-in-water emulsion comprising one or more surfactants, by mixing oil components of the oil-in-water emulsion with aqueous components of the oil-in-water emulsion, wherein the oil components and/or the aqueous components of the oil-in-water emulsion comprises the one or more surfactants;~~

~~b) solubilizing vesicle forming lipids in an acceptable solvent other than water;~~

~~c) adding one or more compounds and one or more penetration enhancing agents to the oil components and/or the aqueous components of step a), and/or the solubilized vesicle forming lipids of step b);~~

~~d) adding the oil-in-water emulsion to the solubilized vesicle forming lipids; and~~

~~e) mixing the oil-in-water emulsion and the solubilized vesicle forming lipids under mixing conditions effective to form the biphasic lipid vesicles comprising a lipid bilayer comprising vesicle forming lipids, and an oil-in-water emulsion entrapped in the biphasic lipid vesicles.~~

~~54. The biphasic lipid vesicle composition of any one of claim 43 to 51, wherein the biphasic lipid vesicle compositions are comprised in a transdermal delivery system.~~

~~55. The biphasic lipid vesicle composition of claim 54, wherein the transdermal delivery system is a patch or a mask sheet.~~

~~56. A method of delivering one or more compounds by administering the biphasic lipid vesicle compositions of any one of claims 1 to 52 topically to the skin or mucosal membrane to a subject.~~

~~57. The method of claim 56 for improving topical delivery of one or more compounds comprising administering an effective amount of the biphasic lipid vesicle compositions of any one of claims 1 to 52 to the skin or mucosal membrane of a subject in need thereof.~~

~~58. The method of claim 56 or 57 for treating or preventing skin conditions related to excessive or defective collagen production in a subject comprising administering to the subject in need thereof, an effective amount of the lipid vesicle cosmetic compositions of any one of claims 1 to 52 to a subject in need thereof.~~

~~59. The method of claim 58 wherein the skin conditions related to excessive or defective collagen is skin aging, skin elasticity, striae, stretchmarks, wrinkles, collagen vascular diseases such as cutaneous scleroderma, morphoea, lupus, rheumatoid arthritis, temporal arteritis, or hereditary collagen diseases such as Ehlers-Danlos syndrome or Marfan's syndrome.~~

~~60. The method of claim 56 for treating a disease, disorder or condition treatable by delivering one or more therapeutic compounds by administering a therapeutically effective amount of the biphasic lipid vesicle pharmaceutical compositions of any one of claims 1 to 52 topically to the skin or mucosal membrane to a subject in need thereof.~~

~~61. The method of claim 60, wherein the disease, disorder or condition treatable by delivering one or more therapeutic compounds by administering a therapeutically effective amount of the biphasic lipid vesicle pharmaceutical compositions topically to the skin or mucosal membrane is skin condition related to excessive or defective collagen production, inflammation, pain, a fungal infection, a viral infection, skin/dermatological conditions, rheumatic conditions, joint conditions, skin aging or canc~~