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 10 or less, wherein the one or more penetration enhancing agents comprise diethylene glycol monooleyl ether, PEG-4 dilaurate, sorbitan monopalmitate, or any combination thereof.

[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 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 10 or less, wherein the one or more penetration enhancing agents comprise diethylene glycol monooleyl ether, PEG-4 dilaurate, sorbitan monopalmitate, or any combination thereof.

2. The composition of claim 1, wherein the one or more penetration enhancing agents are entrapped in the oil-in-water emulsion.

3. The composition of claim 1, wherein the one or more penetration enhancing agents are entrapped in the lipid bilayer and the oil-in-water emulsion.

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

5. The composition of claim 1, wherein the one or more non-ionic surfactants having a hydrophilic-lipophilic balance (HLB) of 10 or less are selected from one or more of polyethylene glycol ethers of fatty alcohols, sorbitan esters, polysorbates, polyethylene glycol fatty acid esters, or any combination thereof.

6. The composition of claim 5, wherein the polyethylene glycol ethers of fatty alcohols are selected from diethylene glycol hexadecyl ether, 2-(2-octadecoxyethoxy)ethanol, diethylene glycol monooleyl ether, polyoxyethylene (3) oleyl ether, polyoxyethylene (5) oleyl ether, or any combination thereof.

7. The composition of claim 5, wherein the polyethylene glycol fatty acid esters are selected from PEG-8 dilaurate, PEG-4 dilaurate, PEG-4 laurate, PEG-8 dioleate, PEG-8 distearate, PEG-8 distearate, PEG-7 glyceryl cocoate, PEG-20 almond glycerides, or any combination thereof.

8. The composition of claim 1, wherein the one or more penetration enhancing agents further comprise terpenes, alkaloids, salicylate derivatives, polycationic surfactants, or any combination thereof.

9. The composition of claim 8, wherein the terpenes are selected from one or more of eugenol, d-limonene, menthol, menthone, farnesol, neridol, camphor, nerol, thymol, or any combination thereof.

10. The composition of claim 8, wherein the salicylate derivatives are selected from one or more of ethyl salicylate, salicylic acid, acetylsalicylic acid, trolamine salicylate, or any combination thereof.

11. The composition of claim 8, wherein the alkaloids are selected from piperine, lobeline, caffeine, theobromine theophylline, nicotine, colchicine, N-methyl pyrrolidone, hygrine, capsaicin, berberine, sanguinarine, histamine, pilocarpine, or any combination thereof.

12. The composition of claim 8, wherein the polycationic surfactants comprise one or more gemini cationic surfactants and the one or more gemini cationic surfactants are of a quaternary ammonium type.

13. The composition of claim 8, wherein the polycationic surfactants comprise polycationic amino acids.

14. The composition of claim 1, wherein the oil-in-water emulsion of the biphasic lipid vesicles is stabilized by one or more additional surfactants comprising polyoxyethylene (10) cetyl ether and polysorbate 80.

15. The composition of claim 1, wherein the vesicle forming lipids are selected from one or more of phospholipids, glycolipids, lecithins, or ceramides.

16. The composition of claim 1, further comprising one or more compounds 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.

17. The composition of claim 16, wherein the one or more compounds comprise a small molecule, protein, peptide, carbohydrate, nucleic acid, vaccine antigen, plant extract, or any combination thereof.

18. The composition of claim 1, wherein the biphasic lipid vesicle formulations further comprise one or more other lipid vesicle components comprising a fatty substance, penetration enhancer, surfactant, solvents, or any combination thereof.

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