Liposomal components

[0041] The term "liposome" as used herein refers to microscopic vesicles or particles made up of one or more lipid bilayers enclosing an internal aqueous medium. To form liposomes, the presence of at least one "vesicle-forming lipid" is needed, which is an amphipathic lipid capable of either forming or being incorporated into a lipid bilayer. Any suitable vesicle-forming lipid may be used to form the lipid bilayer constituting the liposomes. Vesicle-forming lipid includes, but not limited to, phospholipids such as phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidylethanolamine (PE) or phosphatidylserine (PS), and charged lipids, such as a positively charge lipid or a negatively charged lipid.

[0042] The lipid bilayer of the liposome further comprises sterol (e.g., 0-14.99 mole %), said sterol is selected from the group consisting of cholesterol, cholesteryl hemisuccinate, ergosterol, lanosterol, and any combination thereof, but is not limited thereto. In an exemplary embodiment, the sterol is cholesterol.

[0043] In some embodiments, the vesicle-forming lipid is a mixture of a fist phospholipid and a second phospholipid. In certain embodiments, the first phospholipid is phosphatidylcholine (PC), which is selected from the group consisting of hydrogenated egg phosphatidylcholine (HEPC), hydrogenated soy phosphatidylcholine (HSPC), dipalmitoyl phosphatidylcholine (DPPC), distearoyl phosphatidylcholine (DSPC), diarachidoyl phosphatidylcholine, dimyristoyl phosphatidylcholine (DMPC), egg phosphatidylcholine (EPC), soy phosphatidylcholine (SPC), oleoyl palmitoyl phosphatidylcholine, dioleoyl phosphatidylcholine (DOPC), dipetroselinoyl phosphatidylcholine, palmitoylelaidoyl phosphatidylcholine, palmitoyloleoyl phosphatidylcholine, dilauroyl phosphatidylcholine (DLPC), diundecanoyl phosphatidylcholine, didecanoyl phosphatidylcholine, dinonanoyl phosphatidylcholine, and any combination thereof. In other embodiments, the second phospholipid is a polyethylene glycol modified phospholipid, containing a polyethylene glycol having a molecular weight of about 500 to about 10,000 daltons, such as 1,2-distearoly-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG2000), a negatively charged

phospholipid, such as distearoyl phosphatidylglycerol (DSPG), Dipalmitoylphosphatidylglycerol (DPPG) or dimyristoylphosphatidylglycerol (DMPG) or dioleoyl phosphatidylglycerol (DOPG). In an exemplary embodiment, the mole percent of the first phospholipid: cholesterol: the second phospholipid is 75-99:0-14.9: 0.1-25.

[0044] In other embodiments, the vesicle-forming lipids are a mixture of a first phospholipid and a charged lipid. In an exemplary embodiment, vesicle-forming lipids are a mixture of a first phospholipid, a second phospholipid and a charged lipid. The charged lipid, includes stearylamine, 1,2-diole oyl-3-trimethylammonium-propane (DOTAP), 3ß-[N-(N',N'-dimethylaminoethane)-carbamoyl]cholesterol (DC-Cholesterol), N^4-Cholesteryl-Spermine (GL67), dimethyldioctadecylammonium (DDAB), 1,2-di-O-octadecenyl-3-trimethylammonium propane (DOTMA), ethylphosphocholine (ethyl PC) or combination thereof. In another exemplary embodiment, the mole percent of the first phospholipid: cholesterol: charged lipid is 75-99:0-14.9: 0.1-25.

[0045] In an embodiment, the mole % of HSPC, cholesterol, and DSPG in the lipid bilayer is 75-99:0-14.9: 0.1-25. In another embodiment, the mole % of HSPC, cholesterol and DSPE-PEG2000 in the lipid bilayer is 75-99:0-14.9: 0.1-25.

[0046] In one embodiment, the external lipid bilayer of the liposomes further comprises a surfactant, which can be a non-ionic surfactant, a cationic surfactant or a zwitterionic surfactant. A non-ionic surfactant has no formally charged groups in its head. A cationic surfactant carries a net positive charge in its head. A zwitterion surfactant is electrically neutral but carries formal positive and negative charges on different atoms.

[0047] Non-limiting examples of non-ionic surfactant include non-ionic water soluble mono-, di-, and tri-glycerides; non-ionic water soluble mono- and di-fatty acid esters of polyethyelene glycol; non-ionic water soluble sorbitan fatty acid esters (e.g. sorbitan monooleates such as TWEEN 20 (polyoxyethylene 20 sorbitan monooleate), SPAN 80); non-ionic water soluble triblock copolymers (e.g., poly(ethyleneoxide)/poly-(propyleneoxide)/poly(ethyleneoxide)

Claims

1. A pharmaceutical composition, comprising:

   liposomes suspended in an external medium, said liposomes comprising:

   (a) an external lipid bilayer, comprising (i) 75-99 mole percent of a first phospholipid that is a phosphatidylcholine (PC), (ii) 0.1-25 mole percent of a second phospholipid that is a phosphatidylethanolamine (PE) and (iii) 0-14.9 mole percent of a sterol; and

   (b) an internal aqueous medium, comprising iloprost and a bicarbonate salt at a concentration of 50 mM±10% to 600 mM±10%

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2. The pharmaceutical composition of claim 1, wherein the sterol is selected from the group consisting of cholesterol, cholesteryl hemisuccinate, ergosterol, lanosterol, and combination thereof.

3. The pharmaceutical composition of claim 1, wherein the concentration of bicarbonate salt is 200mM±10% to 600 mM±10%.

4. The pharmaceutical composition of claim 1, wherein the PC is HSPC, DSPC, DPPC, DMPC or any combination thereof and the PE is PEG-DSPE.

5. The pharmaceutical composition of claim 1, wherein the potency of said iloprost in the pharmaceutical composition is at least two times more than that of a free weak acid drug.

6. The pharmaceutical composition of claim 1, wherein the PC is HSPC, the sterol is cholesterol and the PE is PEG-DSPE.

7. The pharmaceutical composition of claim 6, wherein the mole percent of HSPC: PEG-DSPE is 98:2.

8. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for

the treatment of pulmonary hypertension.

9. The use of claim8, wherein the medicament is to be administered at least every 6 hours.

10. The use of claim 8, wherein the medicament is to be administered once, twice or three times a day.

11. The use of claim 8, wherein the medicament is to be administered by inhalation.

12. The use of claim 11, wherein the therapeutic effect of said iloprost is maintained for at least 6 hours after administration of the medicament.

13. The use of claim 8, wherein the medicament is to be conjointly administered with at least one other agent effective to treat pulmonary hypertension.

14. The pharmaceutical composition of claim 1, for use in therapy.