tracheal administration of 48 μg/kg of liposomal treprostinil composition (see Measured Data in Figure 1A to 1D). Therefore, the liposomal treprostinil composition of the present invention can be delivered twice a day (BID, every 8, 10 or 12 hours) or three times a day (TID, every 8 hours) (see Simulated Profile in Figure 1A to 1D) while maintaining the therapeutic plasma level of treprostinil.

[0090] Figure 1E shows the measured and simulated PK profiles of free treprostnil solution (at 12 μg/kg) administered every 4 hours, QID. The plasma concentration reached a much higher peak (8.0 ng/mL) within one hour of treprostinil inhalation (T_{max} = 0.083 hr) and dropped below the lower limit of quantification (LLOQ at 25 pg/mL) within 4 hours of treprostinil inhalation (Figure 1E, Measured Data). This pK profile conforms with the dosing schedule listed in the prescribing information of inhaled Tyvaso (treprostinil), which is 4 times daily (QID) every 4 hours (Figure 1E, Simulated Profile).

[0091] The BID or TID dosing schedule of liposomal treprostinil composition lead to a flatter plasma profile and a lower P/T ratio (less than 10) compared to that of the QID dosing schedule of free treprostinil solution (P/T ratio = 121) (see Table 4).

[0092] Table 4: The peak-to-trough (P/T) ratio of liposomal treprostinil composition and free treprostinil solution inhaled by rats at different dosing schedule

Formulation	Applied dose level	Schedule	C_{max} (ng/mL)	C_{last} (ng/mL)	P/T ratio[1]
Liposomal Treprostinil Composition	48 μg/kg	8 hrs, BID	4.936 (at 8.33 h)	2.134 (at 16 h)	2.3
		10 hrs, BID	4.008 (at 10.33 h)	1.075 (at 20 h)	3.7
		12 hrs, BID	3.391 (at 12.33 h)	0.363 (at 24 h)	9.3
		8 hrs, TID	4.936 (at 8.33 h)	2.134 (at 24 h)	2.3
Free Treprostinil Solution	12 μg/kg	4 hrs, QID	7.971 (at 4.08 h)	Below LLOQ[2] (at 8 h)	NA[3]

1: P/T ratio = C_{max}/C_{last}, where C_{max} = highest steady state plasma concentration and C_{last} = lowest steady state plasma concentration between at least two doses.

2: Lower than the limit of quantification (LLOQ = 0.025 ng/mL)

3: Not available because of the undetectable C_{last} 4 hours post dosing.

[0093] **Example 2**: The Effect of Liposomal Iloprost Composition on Iloprost Plasma Level in Healthy Rats

[0094] After intra-tracheal administration of the liposomal iloprost composition (at 60 μg/kg), iloprost plasma concentration reached the peak C_{max} (8.10 ng/mL) within 5 mins of dosing and decreased gradually to 0.32 ng/mL 8 hours post-dosing and 0.17 ng/mL 12 hours post-dosing (Figure 2A to 2D, Measured Data). Therefore, the liposomal iloprost composition can be delivered twice a day (BID, every 6-8 hours) or three times a day (TID, every 6-8 hours) (see Simulated Profile in Figure 2A to 2D) while maintaining therapeutic plasma level of iloprost.

[0095] The rat PK profile of free iloprsost solution (60 μg/kg dose) shows a higher peak plasma concentration (32 ng/mL) was reached at 0.083 hr (T_{max}), similar to that of the liposomal iloprost composition but C_{max} was approximately 4-fold of that of the liposomal iloprost composition . Iloprost plasma concentration dropped below LLOQ (100 pg/mL) within 1 hour post dosing (**Figure 2E**, Measured Data). This pK profile conforms with the dosing schedule listed in the prescribing information of inhaled Ventavis (iloprost), which is 6–9 times daily (QID) every 2 hours (**Figure 2E**, Simulated Profile).

[0096] The BID or TID dosing schedule of liposomal iloprost composition lead to a flatter plasma profile compared to that of the free iloprost solution administered 2 hourly (see Table 5).

[0097] Table 5: The peak-to-trough (P/T) ratio of liposomal iloprost composition and free iloprost solution administered to rats at different dosing schedules

Formulation	Applied dose level	Schedule	C_{max} (ng/mL)	C_{last} (ng/mL)	P/T ratio[1]
Liposomal Iloprost Composition	60 μg/kg	6 hrs, BID	8.431 (at 6.08 h)	0.563 (at 12 h)	15.0
		8 hrs, BID	8.352 (at 8.08 h)	0.428 (at 16 h)	19.5
		6 hrs, TID	8.431 (at 6.08 h)	0.563 (at 18 h)	15.0
		8 hrs, TID	8.352 (at 8.08 h)	0.316 (at 24 h)	26.4
Iloprost Solution	60 μg/kg	2 hrs, 6 times per day	30.750 (at 2.08 h)	Below LLOQ[2] (at 4 h)	NA[3]

1: P/T ratio = C_{max}/C_{last}, where C_{max} = highest steady state plasma concentration and C_{last} = lowest steady state

Claims

1. A pharmaceutical composition, comprising:

   liposomes suspended in an external medium, said liposomes comprising:

   (a) an external lipid bilayer, comprising at least one vesicle-forming phospholipid; and

   (b) an internal aqueous medium, comprising a weak acid drug with a half-life less than 2 hours and a weak acid salt to provide a pH gradient between the internal aqueous medium and the external medium,

wherein following administration of the pharmaceutical composition, at least every six hours produces a peak to trough drug plasma concentration ratio (P/T ratio) of about 1 to about 100.

2. The pharmaceutical composition of claim 1, wherein the external lipid bilayer further comprising a sterol selected from the group consisting of cholesterol, cholesterol hexasuccinate, ergosterol, lanosterol, and combination thereof.

3. The pharmaceutical composition of claim 1, wherein the weak acid salt is a bicarbonate salt.

4. The pharmaceutical composition of claim 1, wherein the weak acid drug is prostaglandin or its analogue.

5. The pharmaceutical composition of claim 4, wherein said prostaglandin is treprostinil or iloprost.

6. The pharmaceutical composition of claim 5, wherein said prostaglandin is iloprost and the P/T ratio is about 5 to about 40.

7. The pharmaceutical composition of claim 5, wherein said prostaglandin is treprostinil and the P/T ratio is about 1 to about 20.

8. The pharmaceutical composition of claim 1, wherein the vesicle-forming lipid is a mixture

of a first phospholipid and a second phospholipid or a mixture of a first phospholipid and a charged lipid.

9. The pharmaceutical composition of claim 8, wherein the first phospholipid is selected from the group consisting of phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidyethanolamine (PE), phosphatidylserine (PS) and any combination thereof, the second phospholipid is a PEG modified phospholipid, a positively charged or a negatively charged phospholipid, and the charged lipid is a positively charged or a negatively charged lipid.

10. The pharmaceutical composition of claim8, wherein the first phospholipid is selected from HSPC, DSPC, DPPC, DMPC or combination thereof and the second phospholipid selected from DSPG, DPPG, DMPG, PEG-DSPE, or combination thereof.

11. The pharmaceutical composition of claim 8, wherein the first phospholipid is selected from HSPC, DSPC, DPPC, DMPC or combination thereof and the charged lipid is stearylamine, 1,2-dioleoyl-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.

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

13. The pharmaceutical composition of claim 1, wherein the weak acid drug is substantially free of a carrier.

14. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for the treatment of pulmonary hypertension.

15. The use of claim 14, wherein the medicament is to be administered at least every 6 hours.

16. The use of claim 14, wherein the medicament is to be administered once, twice or three times a day.

17. The use of claim 14, wherein the medicament is to be administered by inhalation.

18. The use of claim 17, wherein the therapeutic effect of the weak acid drug is maintained for at least 6 hours after administration of the medicament.

19. The use of claim 17, wherein the peak to trough drug plasma concentration ratio (P/T ratio) of about 1 to about 40 is maintained from about 1 hour to about 12 hours after administration of the medicament.

20. The use of claim 14, wherein the medicament is to be conjointly administered with at least one other agent effective to treat pulmonary hypertension.

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