with the required substrate (*i.e.*, Man-1-P). However, the delivery and maintenance of such a systemic supply of Man-1-P is problematic, as extracellular enzymes within bodily fluids degrade Man-1-P when delivered exogenously by oral or intravenous administration. Another problem with exogenously delivered Man-1-P is that its high polarity prevents Man-1-P from penetrating into the cell interior (*i.e.*, cytosol) and thus treating the deficiency in PMM production.

[0009] Derivatives of the polar Man-1-P can be synthesized to make Man-1-P more cell-permeable (US Patent Publication No. 2009/0054353). This approach, however, is also problematic, as the cell-permeable Man-1-P derivatives have been shown to be either unstable for clinical use or cytotoxic via the by-products of the Man-1-P derivatives (Eklund et al., *Glycobiology* 2005, 15: 1084-1093; Rutschow et al. *Bioorg Med Chem* 2002, 10: 4043-4049; and Hardre et al., *Bioorg Med Chem Lett* 2007, 17: 152-155).

[0010] Other potential therapies have focused on inhibiting enzymes that catabolize mannose-6-phosphate (Man-6-P), a precursor to Man-1-P, via the inhibition of phosphomannose isomerases (PMI). The approach focuses on forcing the reaction towards optimizing homeostasis, which with the use of PMI inhibitors, would have been skewed toward production of Man-6-P. These approaches, however, are ineffective as clinical treatment options due to their associated toxicity, off-target side effects, and poor selective tissue penetration.

[0011] Another potential solution is to use a delivery vehicle (*e.g.*, lipid particles) to encapsulate and deliver Man-1-P to the cell interior (*see* WO 2015/053910). However, due to the high charge and polarity of phosphorylated carbohydrates in general, the optimal delivery vehicle must overcome challenges of stability, phosphorylated carbohydrates loading rate and concentration, toxicity, and delivery efficiency.

[0012] Accordingly, unmet needs exist for improved compositions and methods for delivering phosphorylated carbohydrates, such as Man-1-P and Man-6-P, to the cell interior in order to treat disorders, such as a congenital disorder of glycosylation (CDG), to subjects (including, for example, humans) in need of such treatment.

BRIEF SUMMARY

[0012a] In an aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a liposome comprising:

i) 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or a salt thereof;

ii) one or more phospholipids having a polar head group comprising glycerol, choline, phosphate or serine, and two unsaturated fatty acid tails, wherein each unsaturated fatty acid tail comprises a C_{10-28} alkenyl chain; and

iii) polyethylene glycol (PEG) conjugated to at least one phospholipid; and

mannose-1-phosphate or a salt thereof encapsulated in the liposome.

[0012b] In another aspect of the present disclosure, there is provided a liposomal pharmaceutical composition comprising mannose-1-phosphate or a salt thereof, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and DSPE-PEG_{2000}, wherein the molar ratio of DOPE, DOPC and DSPE-PEG_{2000} is 30:67:3.

[0012c] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a congenital disorder of glycosylation (CDG) in a human in need thereof.

[0012d] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in therapy.

[0013] The present disclosure meets the unmet needs described above by providing compositions and kits comprising phosphorylated carbohydrates encapsulated by certain liposomes that address the phosphorylated carbohydrate loading efficiency, cytotoxicity, and

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a liposome comprising:

i) 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or a salt thereof;

ii) one or more phospholipids having a polar head group comprising glycerol, choline, phosphate or serine, and two unsaturated fatty acid tails, wherein each unsaturated fatty acid tail comprises a C_{10-28} alkenyl chain; and

iii) polyethylene glycol (PEG) conjugated to at least one phospholipid; and

mannose-1-phosphate or a salt thereof encapsulated in the liposome.

2. The pharmaceutical composition of claim 1, wherein the phospholipid comprising the polar head group is choline.

3. The pharmaceutical composition of claim 1, wherein the one or more phospholipid having a polar head group is:

1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC);

1,2-dioleoyl-sn-glycero-3-phosphoglycerol (DOPG); or

1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS),

or a salt thereof,

or any combination of the foregoing.

4. The pharmaceutical composition of claim 2, wherein the one or more phospholipids having a polar head group comprise 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) or a salt thereof.

5. The pharmaceutical composition of any one of claims 1-4, wherein the phospholipid conjugated to the PEG is 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)

6. The pharmaceutical composition of any one of claims 1-4, wherein component (iii) of the liposome is DSPE-PEG_{2000}.

7. The pharmaceutical composition of any one of claims 1-6, wherein the liposome does not comprise cholesterol or a cholesterol ester.

8. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 15 to about 30 molar percent.

9. The pharmaceutical composition of claim 8, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

10. The pharmaceutical composition of claim 8, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

11. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 25 to about 30 molar percent.

12. The pharmaceutical composition of claim 11, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

13. The pharmaceutical composition of claim 11, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

14. The pharmaceutical composition of any one of claims 1-7, wherein the DOPE is present in the composition from about 30 to about 60 molar percent.

15. The pharmaceutical composition of claim 14, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 35 to about 75 molar percent.

16. The pharmaceutical composition of claim 14, wherein the one or more phospholipid having a polar head group is DOPC, wherein the DOPC is present in the composition from about 60 to about 65 molar percent.

17. The pharmaceutical composition of any one of claims 1-16, wherein the concentration of mannose-1-phosphate in the liposome is from about 2.5 mM to about 5 mM.

18. The pharmaceutical composition of any one of claims 1-16, wherein the concentration of mannose-1-phosphate in the liposome is from about 5 mM to about 10 mM.

19. The pharmaceutical composition of any one of claims 1-18, wherein the average particle size of the liposomes in the composition is about 0.1 microns.

20. A liposomal pharmaceutical composition comprising mannose-1-phosphate or a salt thereof, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), and DSPE-PEG_{2000}, wherein the molar ratio of DOPE, DOPC and DSPE-PEG_{2000} is 30:67:3.

21. Use of a pharmaceutical composition of any one of claims 1 to 20, in the manufacture of a medicament for treating a congenital disorder of glycosylation (CDG) in a human in need thereof.

22. The use of claim 21, wherein the CDG is CDG-Ia, CDG-Ie, CDG-Ii, CDG-Ik, CDG-Io, GDG-Ip, or DPM2-CDG.

23. A pharmaceutical composition of any one of claims 1 to 20, for use in therapy.