CLAIMS

What is claimed is:

1. A method of treating a subject having diabetes mellitus, the method comprising administering to the subject a composition comprising a lipid-based nanoparticle, wherein the insulin is dispersed within the nanoparticle;

wherein the amount of the insulin in the composition is lower than the amount of free insulin that would be administered to treat the diabetes mellitus in the subject;

wherein the administration results in approximately equivalent or better blood glucose control as afforded by the amount of free insulin that would be administered to treat the diabetes mellitus in subject and does not cause significant hypoglycemia in the subject;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

2. The method of claim 1, wherein the amount of the insulin in the composition causes no significant iatrogenic hyperinsulinemia in the subject.

3. The method of claim 2, wherein the amount of free insulin that would be administered to treat the diabetes mellitus in subject causes significant iatrogenic hyperinsulinemia in the subject.

4. A method of increasing the volume of distribution of an insulin administered to a subject, the method comprising administering to the subject a composition comprising a

lipid-based nanoparticle, wherein the insulin is dispersed within the nanoparticle;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

5. A method of increasing or improving glycemic control in a subject being administered an insulin, the method comprising administering to the subject a composition comprising a lipid-based nanoparticle, wherein the insulin is dispersed within the nanoparticle;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

6. A method of increasing or improving basal glucose control in a subject being administered an insulin, the method comprising administering to the subject a composition

comprising a lipid-based nanoparticle, wherein the insulin is dispersed within the nanoparticle;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

7. The method of claim 6, wherein the insulin comprises bolus insulin.

8. The method of claim 7, wherein the subject is further administered a basal insulin.

9. The method of claim 8, wherein the basal insulin is formulated in a composition comprising a lipid-based nanoparticle, wherein the basal insulin is dispersed within the nanoparticle;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from

the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

10. A method of increasing or improving basal glucose control in a subject being administered an insulin, the method comprising administering in a continuous manner to the subject a composition comprising a lipid-based nanoparticle, wherein the insulin is dispersed within the nanoparticle;

wherein the nanoparticle is enclosed by a bipolar lipid membrane comprising cholesterol, dicetyl phosphate, an amphipathic lipid, and a hepatocyte receptor binding molecule;

wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycerol-[3-phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl), 1,2-dimyristoyl-sn-glycero-3-phosphate, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, 1,2-distearoyl-sn-glycero-3-phosphate, 1,2-dipalmitoyl-sn-glycero-3-phosphate, and 1,2-dipalmitoyl-sn-glycero-3-phosphocholine;

wherein the at least one hepatocyte receptor binding molecule extends outward from the nanoparticle; and

wherein the size of the nanoparticle ranges from about 10 nm to about 150 nm.

11. The method of claim 10, wherein the composition is administered continuously to the subject over a period of at least 24 hours.

12. The method of any of claims 10-11, wherein the composition is administered continuously to the subject using a pump.

13. The method of any of claims 1-12, wherein the subject has a hemoglobin A1c level equal to or greater than 8.5%.

14. The method of any of claims 1-12, wherein the subject has a hemoglobin A1c level lower than 8.5%, optionally wherein the subject has a hemoglobin A1C level equal to or greater than 6.5%.

15. The method of any of claims 1-14, wherein the membrane further comprises at least one agent selected from the group consisting of a stabilizer and stearoyl lysophosphatidylcholine.

16. The method of claim 15, wherein the stabilizer is selected from the group consisting of m-cresol, benzyl alcohol, methyl 4-hydroxybenzoate, thiomersal, and butylated hydroxytoluene (2,6-di-*tert*-butyl-4-methylphenol).

17. The method of any of claims 15-16, wherein the stabilizer ranges from about 10% to about 25 % (w/w) in the membrane.

18. The method of claim 15, wherein the stearoyl lysophosphatidylcholine ranges from about 5% to about 30% (w/w) in the membrane.

19. The method of any of claims 1-14, wherein the insulin is covalently bound to the nanoparticle.

20. The method of any of claims 1-14, wherein the insulin is not covalently bound to the nanoparticle.

21. The method of any of claims 1-14, wherein the insulin is suspended in an aqueous solution comprising a free dissolved insulin that is not dispersed within the nanoparticle.

22. The method of claim 21, wherein the nanoparticle-dispersed insulin and the free dissolved insulin are independently selected from the group consisting of insulin lispro, insulin aspart, regular insulin, insulin glargine, insulin zinc, extended human insulin zinc suspension, isophane insulin, human buffered regular insulin, insulin glulisine, recombinant human regular insulin, recombinant human insulin isophane, and any combinations thereof.

23. The method of any of claims 1-14, wherein the amphipathic lipid comprises at least one selected from the group consisting of 1,2-distearoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-(succinyl).

24. The method of any of claims 1-14, wherein the hepatocyte receptor binding molecule comprises biotin.

25. The method of claim 24, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of N-hydroxysuccinimide (NHS) biotin; sulfo-NHS-biotin; N-hydroxysuccinimide long chain biotin; sulfo-N-hydroxysuccinimide long chain biotin; D-biotin; biocytin; sulfo-N-hydroxysuccinimide-S-S-biotin; biotin-BMCC; biotin-HPDP; iodoacetyl-LC-biotin; biotin-hydrazide; biotin-LC-hydrazide; biocytin hydrazide; biotin cadaverine; carboxybiotin; photobiotin; *ρ*-aminobenzoyl biocytin trifluoroacetate; *ρ*-diazobenzoyl biocytin; biotin DHPE (2,3-diacetoxypropyl 2-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)ethyl phosphate); biotin-X-DHPE (2,3-diacetoxypropyl 2-(6-(5-((3aS,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)hexanamido) ethyl phosphate); 12-((biotinyl)amino)dodecanoic acid; 12-((biotinyl)amino)dodecanoic acid succinimidyl ester; S-biotinyl homocysteine; biocytin-X; biocytin x-hydrazide; biotinethylenediamine; biotin-XL; biotin-X-ethylenediamine; biotin-XX hydrazide; biotin-XX-SE; biotin-XX, SSE; biotin-X-cadaverine; α-(t-BOC)biocytin; N-(biotinyl)-N'-(iodoacetyl) ethylenediamine; DNP-X-biocytin-X-SE; biotin-X-hydrazide; norbiotinamine hydrochloride; 3-(N-maleimidylpropionyl)biocytin; ARP; biotin-l-sulfoxide; biotin methyl ester; biotin-maleimide; biotin-poly(ethyleneglycol) amine; (+) biotin 4-amidobenzoic acid sodium salt; Biotin 2-N-acetylamino-2-deoxy-β-D-glucopyranoside; Biotin-α-D-N-acetylneuraminide; Biotin-α-L-fucoside; Biotin lacto-N-bioside; Biotin–Lewis-A trisaccharide; Biotin–Lewis-Y tetrasaccharide; Biotin-α-D-mannopyranoside; and biotin 6-O-phospho-α-D-mannopyranoside.

26. The method of claim 24, wherein the biotin-containing hepatocyte receptor binding molecule comprises at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

27. The method of any of claims 1-14, wherein the composition further comprises cellulose acetate phthalate, which is at least partially bound to the therapeutic agent dispersed within the nanoparticle.

28. The method of any of claims 1-14, wherein the composition further comprises at least one charged organic molecule bound to the therapeutic agent dispersed within the nanoparticle, wherein the charged organic molecule is at least one selected from the group consisting of protamines, polylysine, poly (arg-pro-thr)$_n$ in a mole ratio of 1:1:1, poly (DL-Ala-poly-L-lys)$_n$ in a mole ratio of 6:1, histones, sugar polymers comprising a primary amino group, polynucleotides with primary amino groups, proteins comprising amino acid residues with carboxyl (COO^-) or sulfhydral (S^-) functional groups, and acidic polymers.

29. The method of any of claims 1-14, wherein the cholesterol ranges from about 5% to about 25% (w/w) in the membrane.

30. The method of any of claims 1-14, wherein the dicetyl phosphate ranges from about 10% to about 25% (w/w) in the membrane.

31. The method of any of claims 1-14, wherein the DSPC ranges from about 40% to about 75% (w/w) in the membrane.

32. The method of any of claims 1-14, wherein the hepatocyte receptor binding molecule ranges from about 0.5% to about 10% (w/w) in the membrane.

33. The method of claim 15, wherein the amount of the stearoyl lysophosphatidylcholine in the membrane is about 5%-30% (w/w) of the amount of DSPC in the membrane.

34. The method of claim 15, wherein the membrane comprises one of the following:

(a) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE;

(b) cholesterol, dicetyl phosphate, DSPC, m-cresol, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE; and

(c) cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, and at least one selected from the group consisting of biotin DHPE and biotin-X-DHPE.

35. The method of claim 15, wherein the membrane comprises cholesterol, dicetyl phosphate, DSPC, stearoyl lysophosphatidylcholine, m-cresol, and biotin DHPE in a % (w/w) ratio selected from the group consisting of:

(a) about 9.4 : 18.1 : 56.8 : 14.1 : 0.0 : 1.5;

(b) about 7.7 : 15.0 : 58.6 : 0.0 : 17.4 : 1.3; and

(c) about 8.4 : 16.2 : 47.5 : 7.6 : 19.0 : 1.3;

36. The method of any of claims 4-14, wherein the subject has diabetes mellitus.

37. The method of any of claims 1-14, wherein the subject has Type 1 diabetes or Type 2 diabetes.