4. SUMMARY

[0056] The present disclosure provides lipoprotein complexes, comprising a protein fraction (*e.g.*, an apolipoprotein fraction) and a lipid fraction, and populations thereof that are especially suited to treating and/or preventing dyslipidemia and diseases, disorders and/or conditions associated with dyslipidemia. It has been discovered that populations of complexes which have greater purity and/or homogeneity, and/or comprise particular ratios of lipids and proteins, as described herein, have increased ability to mobilize cholesterol combined with reduced risk of side effects.

[0056a] The present disclosure provides a composition comprising a population of lipoprotein complexes, each comprising

(a) a lipid fraction comprising at least one neutral lipid and at least one negatively charged lipid; and

(b) an apolipoprotein fraction consisting essentially of an Apolipoprotein A-I ("ApoA-I"),

wherein

(i) at least 95% by weight of the apolipoprotein in the composition is in complexed form;

(ii) at least 95% by weight of the lipid in the composition is in complexed form;

(iii) no more than 5% or the methionine residues in the apolipoprotein are oxidized;

(iv) the size distribution of the lipoprotein complexes is at least 95% homogeneous, as reflected by a single peak in gel permeation chromatography; and

(v) the composition does not contain any detergent.

[0056b] The present disclosure provides a pharmaceutical composition comprising or consisting essentially of a composition as described herein, and one or more pharmaceutically acceptable carriers, diluents and/or excipients.

[0056c] The present disclosure provides a unit dosage form comprising a therapeutically effective amount of a pharmaceutical composition as described herein.

[0056d] The present disclosure provides a method for preparing lipoprotein complexes, comprising:

(a) cooling a starting suspension comprising a lipid component and a protein component from a temperature in a first temperature range to a temperature in a second temperature range, wherein:

(i) the lipid component consists essentially of lipid particles formed by homogenization;

(ii) the protein component consists essentially of lipid-binding peptides and/or lipid-binding proteins and, optionally, a lipid in an amount that is 10% or less by weight of the total amount of lipid in the starting suspension;

(iii) the starting suspension is the product of a process comprising combining the lipid component and the protein component;

(iv) the lipid:protein molar ratio in said starting suspension is from about 2:1 to about 200:1; and

(v) said first temperature range includes temperatures no less than 10 degrees below and no more than 15 degrees above the transition temperature of said protein component and said second temperature range includes temperatures no less than 10 degrees below and no more than 5 degrees above the transition temperature of said lipid component;

(b) heating the cooled suspension of (a) from a temperature in said second temperature range to a temperature in said first temperature range;

(c) cooling said heated suspension of (b) from a temperature in said first temperature range to a temperature in said second temperature range; and

(d) repeating steps (b) and (c) until at least 80% of the protein component is incorporated into lipoprotein complexes, thereby forming lipoprotein complexes.

[0056e] The present disclosure provides a method for making a pharmaceutical composition, comprising:

(a) preparing a population of lipoprotein complexes according to the method as described herein; and

(b) combining said population of lipoprotein complexes with one or more pharmaceutically acceptable excipients.

[0056f] The present disclosure provides the use of a composition as described herein in the manufacture of a medicament for the treatment of a dyslipidemic disorder.

[0057] The lipoprotein complexes comprise a protein fraction (*e.g.*, an apolipoprotein fraction) and a lipid fraction (*e.g.*, a phospholipid fraction). The protein fraction includes one or more lipid-binding proteins, such as apolipoproteins, peptides, or apolipoprotein peptide analogs or mimetics capable of mobilizing cholesterol when present in a lipoprotein complex. Non-limiting examples of such apolipoproteins and apolipoprotein peptides include preproapoliproteins, preproApoA I, proApoA-I, ApoA-I, preproApoA-II, proApoA-II, ApoA-II, preproApoA-IV, proApoA- IV, ApoA-IV, ApoA-V, preproApoE, proApoE, ApoE, preproApoA-I_M, proApoA-I_M, ApoA-I_M, preproApoA-I_P, proApoA-I_P, ApoA-I_P, preproApoA-I_Z, proApoA-I_Z, and ApoA-I_Z. The apolipoprotein(s) can be in the form of monomers, dimers, or trimers, or mixtures thereof. In a specific embodiment, the apolipoprotein fraction consists essentially of ApoA-I, most preferably of a single isoform. ApoA-I in lipoprotein complexes can have at least 90% or at least 95% sequence identity to a protein corresponding to amino acids 25 to 267 of SEQ ID NO:1. Optionally, ApoA-I further comprises an aspartic acid at the position corresponding to the full length ApoA-I amino acid 25 of SEQ ID NO:1 (and position 1 of the mature protein). Preferably, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% of the ApoA-I is correctly processed, mature protein (*i.e.*, lacking the signal and propeptide sequences) and not oxidized, deamidated and/or truncated.

[0058] The present disclosure also provides mammalian host cells engineered to express ApoA-I, cell cultures comprising ApoA-I, and methods of producing mature, biologically active ApoA-I. It has been discovered that it is possible to engineer mammalian host cells to express large quantities of mature ApoA-I, that is substantially free of both immature ApoA-I (proApoA-I) and truncated forms of ApoA-I generated by protease degradation. These results are surprising. First, host cell machinery for protein processing could be expected to be overwhelmed by

What Is Claimed Is:

1. A population of lipoprotein complexes, each comprising a lipid fraction and an apolipoprotein fraction consisting essentially of an Apolipoprotein A-I ("ApoA-I"), wherein the lipoprotein complexes are at least 95% homogeneous, as reflected by a single peak in gel permeation chromatography.

2. The population of claim 1, wherein the lipoprotein complexes are at least 97% homogeneous, as reflected by a single peak in gel permeation chromatography.

3. The population of claim 1 or claim 2, wherein at least 98% by weight of the ApoA-I in the population is untruncated ApoA-I.

4. The population of any one of claims 1 to 3, wherein at least 95% of the lipoprotein complexes are in the form of particles of 4 nm to 15 nm in size, 6 nm to 15 nm in size, 4 nm to 12 nm in size, 6 nm to 12 nm in size, or 8 nm to 12 in size as measured by gel permeation chromatography ("GPC") or dynamic light scattering ("DLS").

5. The population of any one of claims 1 to 4, wherein at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% by weight over ApoA-I in said population is in mature form.

6. The population of any one of claims 1 to 4, wherein no more than 25%, no more than 20%, no more than 15%, no more than 10% or no more than 5% by weight of ApoA-I in said population is in immature form.

7. The population of any one of claims 1 to 6, wherein no more than 10%, no more than 5%, no more than 3%, no more than 2% or no more than 1% of each of methionine 112 and methionine 148 in said ApoA-I in said population is oxidized.

8. The population of any one of claims 1 to 7, wherein no more than 15%, no more than 10%, no more than 5%, no more than 4%, no more than 3%, no more than 2% or no more than 1% of the amino acids of the ApoA-I in said population is deamidated.

9. The population of any one of claims 1 to 8, wherein the population contains no more than 1 EU, no more than 0.5 EU, no more than 0.3 EU or no more than 0.1 EU of endotoxin per milligram of ApoA-I.

10. The population of any one of claims 1 to 9, wherein the population contains no more than 100 picograms, no more than 50 picograms, no more than 25 picograms, no more than 10 picograms or no more than 5 picograms host cell DNA per milligram of ApoA-I.

11. The population of any one of claims 1 to 10, wherein the population contains no more than 500 nanograms, no more than 200 nanograms, no more than 100 nanograms, no more than 50 nanograms, or no more than 20 nanograms host cell protein per milligram of ApoA-I.

12. The population of any one of claims 1 to 11, wherein the population contains no more than 200 pm, no more than 100 ppm, or no more than 50 ppm of a non-aqueous solvent and/or does not contain any detergent.

13. The population of any one of claims 1 to 12 in which no more than 15%, or no more than 10%, no more than 5% or no more than 2% by weight of the lipid in the lipid fraction in said complexes is cholesterol.

14. The population of any one of claims 1 to 13, wherein said ApoA-I is a human ApoA-I protein.

15. The population of any one of claims 1 to 14, wherein said ApoA-I is a recombinant ApoA-I.

16. The population of any one of claims 1 to 15, wherein said ApoA-I has at least 95% sequence identity to a protein corresponding to amino acids 25 to 267 of SEQ ID NO: 1.

17. The population of any one of claims 1 to 15, wherein said lipid fraction comprises neutral lipids.

18. The population of claim 17, wherein said neutral lipids consist essentially of sphingomyelin.

19. The population of claim 17 or claim 18, wherein the lipid fraction further comprises negatively charged lipids.

20. The population of claim 19, wherein the negatively charged lipids consist essentially of 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] ("DPPG").

21. The population of claim 19 or claim 20 which comprises negatively charged lipids, wherein the molar ratio of the components of the negatively charged lipid to the neutral lipid to the ApoA-1 in the population is 2-6:90-120:1.

22. The population of any one of claims 1 to 21, wherein said lipid fraction consists essentially of 95 to 99 weight % neutral phospholipid and 1 to 5 weight % negatively charged phospholipid.

23. The population claim 22, wherein said lipid fraction consists essentially of 96 to 98 weight % neutral phospholipid and 2 to 4 weight % negatively charged phospholipid.

24. The population of claim 23, wherein said lipid fraction consists essentially of 97 weight % neutral phospholipid and 3 weight % negatively charged phospholipid.

25. The population of claim 24, wherein the neutral lipid is natural sphingomyelin or synthetic sphingomyelin, optionally wherein the lipid has a peroxide value of less than 5 meq O/kg, less than 4 meq O/kg, less than 3 meq O/kg, or less than 2 meq O/kg.

26. The population of claim 25 in which the sphingomyelin is egg-sphingomyelin.

27. The population of any one of claims 24 to 26, wherein the negatively charged phospholipid comprises phosphatidylglycerol.

28. The population of claim 27 in which the negatively charged phospholipid comprises or consists of a salt of 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)] (DPPG).

29. The population of any one of claim 1 to 28 which has an apolipoprotein fraction-to-phospholipid fraction ratio ranging from 1:2 to about 1:3 by weight.

30. The population of any one of claims 1 to 29, produced by a process that does not comprise a size fractionation step for purifying the lipoprotein complexes.

31. A composition comprising a population according to any one of claims 1 to 30.

32. A composition comprising two, three, or four populations according to any one of claim 1 to 30.

33. The composition according to claim 31 or claim 32, said composition comprising no more than 15%, no more than 12%, no more than 10%, no more than 9%, no more than 8%, no more than 7%, no more than 6%, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1% of the lipoprotein in the composition is in uncomplexed form.

34. The composition according to any one of claims 31 to 33, said composition comprising no more than 15%, no more than 12%, no more than 10%, no more than 9%, no more than 8%, no more than 7%, no more than 6%, no more than 5%, no more than 4%, no more than 3%, no more than 2%, no more than 1% of the lipid in the composition is in uncomplexed form.

35. The composition according to any one of claims 31 to 34, comprising a first population which comprises lipoprotein complexes having 2 ApoA-I molecules or ApoA-I equivalents per lipoprotein complex.

36. The composition according to claim 35, comprising a second population which comprises lipoprotein complexes having 3 or 4 ApoA-I molecules or ApoA-I equivalents per lipoprotein complex and, optionally, a third population which comprises lipoprotein complexes having 4 or 3 ApoA-I molecules or ApoA-I equivalents per lipoprotein complex, respectively.

37. The composition according to any one of claims 31 to 36, further comprising one or more pharmaceutically acceptable carriers, diluents and/or excipients.

38. A pharmaceutical composition comprising or consisting essentially of a population of lipoprotein complexes according to any one of claims 1 to 30, and one or more pharmaceutically acceptable carriers, diluents and/or excipients.

39. A unit dosage form comprising a therapeutically effective amount of a pharmaceutical composition of claim 38.

40. A method for preparing lipoprotein complexes, comprising:

(a) cooling a starting suspension comprising a lipid component and a protein component from a temperature in a first temperature range to a temperature in a second temperature range, wherein:

(i) the lipid component consists essentially of lipid particles formed by homogenization;

(ii) the protein component consists essentially of lipid-binding peptides and/or lipid-binding proteins that have not been subject to homogenization and, optionally, a lipid in an amount that is 10% or less by weight of the total amount of lipid in the starting suspension;

(iii) the starting suspension is the product of a process comprising combining the lipid component and the protein component;

(b) heating the cooled suspension of (a) from a temperature in said second temperature range to a temperature in said first temperature range;

(c) cooling said heated suspension of (b) from a temperature in said first temperature range to a temperature in said second temperature range; and

(d) repeating steps (b) and (c) until at least 80% of the protein component is incorporated into lipoprotein complexes, thereby forming lipoprotein complexes.

41. The method of claim 40, in which steps (b) and (c) are repeated until at least 85%, at least 90%, or at least 95% of the protein component is incorporated into lipoprotein complexes.

42. The method of claim 40 or claim 41, in which steps (b) and (c) are repeated at least three times.

43. The method of any one of claims 40 to 42, in which steps (b) and (c) are repeated until lipoprotein complexes of 4 nm to 15 nm in diameter are obtained, as measured by gel filtration chromatography.

44. The method of any one of claims 40 to 43, in which steps (b) and (c) are repeated until the lipoprotein complexes are at least 85%, 90% or 95% homogeneous, as reflected by a single peak in gel permeation chromatography.

45. The method of claim 44, in which steps (b) and (c) are repeated until the lipoprotein complexes are at least 97% homogeneous, as reflected by a single peak in gel permeation chromatography.

46. The method of any one of claims 40 to 45, wherein:

said first temperature range includes temperatures no less than 10 degrees below and no more than 15 degrees above the transition temperature of said protein component; and/or

said second temperature range includes temperatures no less than 10 degrees below and no more than 5 degrees above the transition temperature of said lipid component;

47. The method of any one of claims 40 to 46, wherein said protein component comprises lipid-binding proteins, optionally wherein said protein component consists essentially of Apolipoprotein A-I (ApoA-I).

48. The method of any one of claims 40 to 47, wherein said lipid component comprises neutral lipids, optionally wherein said neutral lipids consist essentially of sphingomyelin.

49. The method of claim 48, wherein the starting suspension further comprises negatively charged lipids, optionally wherein the negatively charged lipids consist essentially of 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)].

50. The method of claim 49, wherein the molar ratio of the components of the negatively charged lipid to the neutral lipid to the lipid-binding peptides and/or lipid binding proteins in the starting suspension is 2-6:90-120:1, the moles of lipid-binding peptides and/or lipid binding proteins defined in ApoA-I equivalents.

51. The method of claim 49 or claim 50, wherein the negatively charged lipids are pre-complexed with the lipid-binding peptides and/or lipid-binding proteins.

52. The method of claim 51, further comprising the step of forming the protein component by a process comprising combining the lipid-binding peptides and/or lipid-binding proteins and the negatively charged lipids.

53. The method of any one of claims 40 to 52, wherein the lipid:protein molar ratio in said starting suspension is from about 2:1 to about 200:1 or wherein the lipoprotein:total phospholipid wt:wt ratio is 1:2.7.

54. The method of any one of claims 40 to 53, further comprising, prior to step (a), the step of forming said starting suspension by a process comprising combining the lipid component and the protein component.

55. The method of claim 54, wherein the solution of the lipid component and the protein component are each preheated at a temperature in said first range.

56. The method of claim 54 or claim 55, which further comprises, prior to the step of forming the starting suspension, the step of forming the lipid particles using high pressure homogenization.

57. The method of any one of claims 40 to 56, which further comprises the step of lyophilizing the resulting lipoprotein complexes.

58. The method of any one of claims 40 to 57, wherein the starting suspension does not contain detergent.

59. The method of any one of claims 40 to 58, wherein the lipid component consists essentially of particles of lipids formed by a process comprising high pressure homogenization.

60. The method of claim 59, wherein the high pressure homogenization comprises microfluidization.

61. A method for making a pharmaceutical composition, comprising:

(a) preparing a population of lipoprotein complexes according to the method of any one of claims 40 to 60; and

(b) combining said population of lipoprotein complexes with one or more pharmaceutically acceptable excipients.

62. Use of a population of lipoprotein complexes according to any one of claims 0 to 30 or a composition according to any one of claims 31 to 37 in the manufacture of a medicament for the treatment of a dyslipidemic disorder.

What Is Claimed Is:

1. A composition comprising a population of lipoprotein complexes, each comprising

(a) a lipid fraction comprising at least one neutral lipid and at least one negatively charged lipid; and

(b) an apolipoprotein fraction consisting essentially of an Apolipoprotein A-I ("ApoA-I"),

wherein

(i) at least 95% by weight of the apolipoprotein in the composition is in complexed form;

(ii) at least 95% by weight of the lipid in the composition is in complexed form;

(iii) no more than 5% or the methionine residues in the apolipoprotein are oxidized;

(iv) the size distribution of the lipoprotein complexes is at least 95% homogeneous, as reflected by a single peak in gel permeation chromatography; and

(v) the composition does not contain any detergent.

2. The composition of claim 1, wherein the size distribution of the lipoprotein complexes is at least 97% homogeneous, as reflected by a single peak in gel permeation chromatography.

3. The composition of claim 1 or claim 2, wherein at least 98% by weight of the ApoA-I in the composition is untruncated ApoA-I.

4. The composition of any one of claims 1 to 3, wherein at least 95% of the lipoprotein complexes are in the form of particles of 4 nm to 15 nm in size, 6 nm to 15 nm in size, 4 nm to 12 nm in size, 6 nm to 12 nm in size, or 8 nm to 12 in size as measured by gel permeation chromatography ("GPC") or dynamic light scattering ("DLS").

5. The composition of any one of claims 1 to 4, wherein at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% by weight of the ApoA-I in said composition is in mature form.

6. The composition of any one of claims 1 to 4, wherein no more than 25%, no more than 20%, no more than 15%, no more than 10% or no more than 5% by weight of ApoA-I in said composition is in immature form.

7. The composition of any one of claims 1 to 6, wherein no more than 5%, no more than 3%, no more than 2% or no more than 1% of each of methionine 112 and methionine 148 in said ApoA-I in said composition is oxidized.

8. The composition of any one of claims 1 to 7, wherein no more than 15%, no more than 10%, no more than 5%, no more than 4%, no more than 3%, no more than 2% or no more than 1% of the amino acids of the ApoA-I in said composition is deamidated.

9. The composition of any one of claims 1 to 8, wherein the composition contains no more than 1 EU, no more than 0.5 EU, no more than 0.3 EU or no more than 0.1 EU of endotoxin per milligram of ApoA-I.

10. The composition of any one of claims 1 to 9, wherein the composition contains no more than 100 picograms, no more than 50 picograms, no more than 25 picograms, no more than 10 picograms or no more than 5 picograms host cell DNA per milligram of ApoA-I.

11. The composition of any one of claims 1 to 10, wherein the composition contains no more than 500 nanograms, no more than 200 nanograms, no more than 100 nanograms, no more than 50 nanograms, or no more than 20 nanograms host cell protein per milligram of ApoA-I.

12. The composition of any one of claims 1 to 11, wherein the composition contains no more than 200 pm, no more than 100 ppm, or no more than 50 ppm of a non-aqueous solvent.

13. The composition of any one of claims 1 to 12 in which no more than 15%, or no more than 10%, no more than 5% or no more than 2% by weight of the lipid in the lipid fraction in said complexes is cholesterol.

14. The composition of any one of claims 1 to 13, wherein said ApoA-I is a human ApoA-I protein.

15. The composition of any one of claims 1 to 14, wherein said ApoA-I is a recombinant ApoA-I.

16. The composition of any one of claims 1 to 15, wherein said ApoA-I has at least 95% sequence identity to a protein corresponding to amino acids 25 to 267 of SEQ ID NO: 1.

17. The composition of any one of claims 1 to 16, wherein said neutral lipid consists essentially of sphingomyelin.

18. The composition of any one of claims 1 to 17, wherein the negatively charged lipid consists essentially of 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)] ("DPPG").

19. The composition of any one of claims 1 to 18, wherein the molar ratio of the components of the negatively charged lipid to the neutral lipid to the ApoA-I in the composition is 2-6:90-120:1.

20. The composition of any one of claims 1 to 19, wherein said lipid fraction consists essentially of 95 to 99 weight % neutral phospholipid and 1 to 5 weight % negatively charged phospholipid.

21. The composition claim 20, wherein said lipid fraction consists essentially of 96 to 98 weight % neutral phospholipid and 2 to 4 weight % negatively charged phospholipid.

22. The composition of claim 21, wherein said lipid fraction consists essentially of 97 weight % neutral phospholipid and 3 weight % negatively charged phospholipid.

23. The composition of claim 22, wherein the neutral lipid is natural sphingomyelin or synthetic sphingomyelin, optionally wherein the lipid has a peroxide value of less than 5 meq O/kg, less than 4 meq O/kg, less than 3 meq O/kg, or less than 2 meq O/kg.

24. The composition of claim 23 in which the sphingomyelin is egg-sphingomyelin.

25. The composition of any one of claims 22 to 24, wherein the negatively charged phospholipid comprises phosphatidylglycerol.

26. The composition of claim 25 in which the negatively charged phospholipid comprises or consists of a salt of 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)] (DPPG).

27. The composition of any one of claim 1 to 26 which has an apolipoprotein fraction-to-phospholipid fraction ratio ranging from 1:2 to about 1:3 by weight.

28. The composition of any one of claims 1 to 27, produced by a process that does not comprise a size fractionation step for purifying the lipoprotein complexes.

29. The composition according to any one of claims 1 to 28, in which at least 97% of the lipoprotein is in complexed form.

30. The composition according to any one of claims 1 to 29, in which at least 97%, at least 98%, at least 99% or 100% of the lipid is in complexed form.

31. A pharmaceutical composition comprising or consisting essentially of a composition according to any one of claims 1 to 30, and one or more pharmaceutically acceptable carriers, diluents and/or excipients.

32. A unit dosage form comprising a therapeutically effective amount of a pharmaceutical composition of claim 31.

33. A method for preparing lipoprotein complexes, comprising:

(a) cooling a starting suspension comprising a lipid component and a protein component from a temperature in a first temperature range to a temperature in a second temperature range, wherein:

(i) the lipid component consists essentially of lipid particles formed by homogenization;

(ii) the protein component consists essentially of lipid-binding peptides and/or lipid-binding proteins and, optionally, a lipid in an amount that is 10% or less by weight of the total amount of lipid in the starting suspension;

(iii) the starting suspension is the product of a process comprising combining the lipid component and the protein component;

(iv) the lipid:protein molar ratio in said starting suspension is from about 2:1 to about 200:1; and

(v) said first temperature range includes temperatures no less than 10 degrees below and no more than 15 degrees above the transition temperature of said protein component and said second temperature range includes temperatures no less than 10 degrees below and no more than 5 degrees above the transition temperature of said lipid component;

(b) heating the cooled suspension of (a) from a temperature in said second temperature range to a temperature in said first temperature range;

(c) cooling said heated suspension of (b) from a temperature in said first temperature range to a temperature in said second temperature range; and

(d) repeating steps (b) and (c) until at least 80% of the protein component is incorporated into lipoprotein complexes, thereby forming lipoprotein complexes.

34. The method of claim 33, in which steps (b) and (c) are repeated until at least 85%, at least 90%, or at least 95% of the protein component is incorporated into lipoprotein complexes.

35. The method of claim 33 or claim 34, in which steps (b) and (c) are repeated at least three times.

36. The method of any one of claims 33 to 35, in which steps (b) and (c) are repeated until lipoprotein complexes of 4 nm to 15 nm in diameter are obtained, as measured by gel filtration chromatography.

37. The method of any one of claims 33 to 36, in which steps (b) and (c) are repeated until the lipoprotein complexes are at least 85%, 90% or 95% homogeneous, as reflected by a single peak in gel permeation chromatography.

38. The method of claim 37, in which steps (b) and (c) are repeated until the lipoprotein complexes are at least 97% homogeneous, as reflected by a single peak in gel permeation chromatography.

39. The method of any one of claims 33 to 38, wherein said protein component consists essentially of lipid binding proteins and/or lipid binding peptides that have not been subject to homogenization.

40. The method of any one of claims 33 to 39, wherein said protein component comprises lipid-binding proteins, optionally wherein said protein component consists essentially of Apolipoprotein A-I (ApoA-I).

41. The method of any one of claims 33 to 40, wherein said lipid component comprises neutral lipids, optionally wherein said neutral lipids consist essentially of sphingomyelin.

42. The method of claim 41, wherein the starting suspension further comprises negatively charged lipids, optionally wherein the negatively charged lipids consist essentially of 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)].

43. The method of claim 42, wherein the molar ratio of the components of the negatively charged lipid to the neutral lipid to the lipid-binding peptides and/or lipid binding proteins in the starting suspension is 2-6:90-120:1, the moles of lipid-binding peptides and/or lipid binding proteins defined in ApoA-I equivalents.

44. The method of claim 42 or claim 43, wherein the negatively charged lipids are pre-complexed with the lipid-binding peptides and/or lipid-binding proteins.

45. The method of claim 44, further comprising the step of forming the protein component by a process comprising combining the lipid-binding peptides and/or lipid-binding proteins and the negatively charged lipids.

46. The method of any one of claims 33 to 45, wherein the lipoprotein:total phospholipid wt:wt ratio is 1:2.7.

47. The method of any one of claims 33 to 46, further comprising, prior to step (a), the step of forming said starting suspension by a process comprising combining the lipid component and the protein component.

48. The method of claim 47, wherein the solution of the lipid component and the protein component are each preheated at a temperature in said first range.

49. The method of claim 47 or claim 48, which further comprises, prior to the step of forming the starting suspension, the step of forming the lipid particles using high pressure homogenization.

50. The method of any one of claims 33 to 49, which further comprises the step of lyophilizing the resulting lipoprotein complexes.

51. The method of any one of claims 33 to 50, wherein the starting suspension does not contain detergent.

52. The method of any one of claims 33 to 51, wherein the lipid component consists essentially of particles of lipids formed by a process comprising high pressure homogenization.

53. The method of claim 52, wherein the high pressure homogenization comprises microfluidization.

54. A method for making a pharmaceutical composition, comprising:

(a) preparing a population of lipoprotein complexes according to the method of any one of claims 33 to 53; and

(b) combining said population of lipoprotein complexes with one or more pharmaceutically acceptable excipients.

55. Use of a composition according to any one of claims 1 to 30 in the manufacture of a medicament for the treatment of a dyslipidemic disorder.