formulations, which lose several of their desired properties including low polydispersity, small particle size, high percentage of encapsulation, and in vivo efficacy upon reconstitution after conventional lyophilization techniques. Thus, new solutions are needed for providing lyophilized lipid nanoparticle compositions that show a maintained integrity and efficacy upon reconstitution.

SUMMARY

[0008] The present disclosure provides lyophilization methods that result in a preservation of lipid nanoparticle integrity, integrity of the encapsulated nucleic acid, the particle size of the lipid nanoparticles within an acceptable degree of pre-lyophilized particle size, and good polydispersity of the nanoparticles. The methods stem from the discovery that specialized excipients can be added to a pretreated suspension of the nanoparticles prior to subjecting the suspension to a lyophilization process. In addition, lyophilization parameters are employed in combination with these excipients to achieve high quality lyophilized lipid nanoparticle product. The lyophilized product is easily reconstituted and readily administered as a pharmaceutical preparation.

[0008a] In an aspect of the present disclosure, there is provided a lyophilized composition comprising lipid nanoparticles encapsulating an RNA, poloxamer, potassium sorbate, and a sugar.

[0008b] In another aspect, there is provided a method of preserving a lyophilized composition as defined above comprising storing the lyophilized product at a temperature of about 2 °C to about 8 °C.

[0008c] In another aspect, there is provided a method of preserving a lyophilized composition as defined above comprising storing the lyophilized product at a temperature of about -20 °C.

[0008d] In another aspect, there is provided a method of reconstituting a lyophilized composition as defined above comprising adding a liquid medium to the lyophilized composition.

[0008e] In another aspect, there is provided a use of a lyophilized composition as defined above reconstituted in a liquid medium in the preparation of a medicament for the treatment of a disease.

[0009] In some ~~embodiments~~examples, a method of lyophilizing a composition comprising lipid nanoparticles encapsulating an RNA is provided comprising the steps of providing a suspension of the lipid nanoparticles in a liquid medium, adjusting the liquid

medium thereby forming a pretreated suspension comprising at least one excipient selected from potassium sorbate, thiosulfate, sodium benzoate, and iodixanol; and subjecting the pretreated suspension to a lyophilization process.

[0010] In another example~~embodiment~~, a lyophilized composition is provided comprising lipid nanoparticles encapsulating a nucleic acid and one or more excipients selected from potassium sorbate, thiosulfate, sodium benzoate, and iodixanol.

[0011] In another examples~~embodiments~~, a method of preserving a lyophilized composition of the disclosure is provided comprising storing the lyophilized product at a temperature of about -20 °C to about 8 °C. In some examples~~embodiments~~, a method of preserving a lyophilized composition of the disclosure is provided comprising storing the lyophilized product at a temperature of about -20 °C to about 25 °C. In some examples~~embodiments~~, the lyophilized product is stored at about -20 °C. In some examples~~embodiments~~, the lyophilized product is stored from about 2 °C to about 8 °C. In some examples~~embodiments~~, the lyophilized product is stored from about 20 °C to about 25 °C.

[0012] In another examples~~embodiments~~, a method of reconstituting a lyophilized composition of the disclosure is provided comprising adding a liquid medium to the lyophilized composition.

[0013] In another examples~~embodiments~~, a method of treating a disease or disorder in a subject is provided comprising administering to the subject a lyophilized composition of the disclosure reconstituted in a liquid medium.

[0014] Additional features and advantages of the subject technology will be set forth in the description below, and in part will be apparent from the description, or may be learned by practice of the subject technology. The advantages of the subject technology will be realized and attained by the written description and examples~~embodiments~~ hereof.

[0015] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the subject technology.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] **Figure 1** shows the characterization (particle size, (PS) polydispersity (PDI), and percent encapsulation (Encap (%)) of reconstituted lipid nanoparticles prepared according to the experiments described in Example 3 for formulations prepared at a concentration of 1 mg RNA/mL.

[0017] **Figure 2A** shows particle size measurements (bar chart) and percent encapsulation (circles) for formulations prepared using P188 poloxamer added to the suspension pre-lyophilization as described in Example 3.

[0018] **Figure 2B** shows particle size measurements (bar chart) and percent encapsulation (circles) for formulations prepared using P188 poloxamer added to the formulation post-lyophilization as described in Example 3.

[0019] **Figure 3** shows the concentration dependence for lipid nanoparticle concentration (0.25, 0.5, and 1.0 mg RNA/mL) for particle size (bar chart) and percent encapsulation (circles) for P188 formulations treated post-lyophilization at different concentrations of P188 as described in Example 3.

[0020] **Figure 4** shows human erythropoietin (hEPO) expression levels for selected reconstituted formulations in comparison to the freeze-thaw control and PBS negative control as described in Example 12.

WHAT IS CLAIMED IS:

1. A method of lyophilizing a composition comprising lipid nanoparticles encapsulating an RNA, the method comprising the steps of:

a. providing a suspension of the lipid nanoparticles in a liquid medium, wherein the liquid medium comprises about 4% w/v to about 22% w/v of a saccharide; and

b. adjusting the liquid medium thereby forming a pretreated suspension comprising at least one excipient selected from potassium sorbate, thiosulfate, sodium benzoate, and iodixanol.

2. The method of claim 1, further comprising step (c):

c. subjecting the pretreated suspension to a lyophilization process comprising:

i. an initial freezing step conducted at a temperature of -48 ± 8 °C and at atmospheric pressure;

ii. a primary drying step conducted at a temperature in the range of -20 ± 2 °C to -48 ± 2 °C and at a pressure in the range of about 25 mTorr to about 100 mTorr; and

iii. a secondary drying step conducted at a temperature in the range of 5 ± 2 °C to 30 ± 2 °C and at a pressure in the range of about 30 mTorr to about 300 mTorr.

3. The method of claim 1, further comprising step (c):

c. subjecting the pretreated suspension to a lyophilization process comprising:

i. an initial freezing step conducted at a temperature of -48 ± 8 °C and at atmospheric pressure;

ii. a primary drying step conducted at a pressure of about 0.03 to about 0.08 mbar and starting at a temperature -48 ± 8 °C and ramping to a temperature of 0 ± 2 °C over a period in the range of about 40 to about 75 hours; and

iii. a secondary drying step conducted at a pressure of about 0.03 to about 0.08 mbar and starting at a temperature 0 ± 2 °C and ramping to a temperature of about 25 ± 3 °C over a period in the range of about 30 to about 50 hours.

4. The method of any one of claims 1 to 3, wherein the liquid medium is an aqueous medium.

5. The method of any of the preceding claims, wherein the RNA in the suspension has a concentration in the range of about 0.05 mg/mL to about 2.0 mg/mL.

6. The method of claim 5, wherein the RNA in the suspension has a concentration in the range of about 0.075 mg/mL to about 0.3 mg/mL.

7. The method of claim 5, wherein the RNA in the suspension has a concentration in the range of about 0.1 mg/mL to about 1.5 mg/mL.

8. The method of claim 5, wherein the RNA in the suspension has a concentration in the range of about 0.1 mg/mL to about 1.0 mg/mL.

9. The method of claim 5, the RNA in the suspension has a concentration in the range of about 0.1 mg/mL to about 0.5 mg/mL.

10. The method of any one of the preceding claims, wherein a total lipid to RNA weight ratio in the suspension is about 50:1 to about 10:1.

11. The method of claim 10, wherein the total lipid to RNA weight ratio in the suspension is about 40:1 to about 20:1.

12. The method of claim 10, wherein the total lipid to RNA weight ratio in the suspension is about 35:1 to about 25:1.

13. The method of any one of the preceding claims, wherein the pretreated suspension comprises thiosulfate.

14. The method of claim 13, wherein the thiosulfate is sodium thiosulfate or potassium thiosulfate.

15. The method of claim 13, wherein the thiosulfate has a concentration of about 0.025% w/v to about 1.0% w/v.

16. The method of claim 13, wherein the thiosulfate has a concentration of about 0.025% w/v to about 0.75% w/v.

17. The method of claim 13, wherein the thiosulfate has a concentration of about 0.025% w/v to about 0.5% w/v.

18. The method of claim 13, wherein the thiosulfate has a concentration of about 0.05% w/v to about 0.3% w/v.

19. The method of claim 13, wherein the thiosulfate has a concentration of about 0.05% w/v to about 0.25% w/v.

20. The method of any one of the preceding claims, wherein the pretreated suspension comprises potassium sorbate.

~~21. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.01 M to about 0.5 M.~~

~~22. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.02 M to about 0.4 M.~~

~~23. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.025 M to about 0.3 M.~~

~~24. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.03 M to about 0.2 M.~~

~~25. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.035 M to about 0.1 M.~~

~~26. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.04 M to about 0.08 M.~~

~~27. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.01 M to about 0.05 M.~~

~~28. The method of claim 20, wherein the potassium sorbate has a concentration of about 0.02 M to about 0.04 M.~~

~~29. The method of any one of the preceding claims, wherein the pretreated suspension comprises iodixanol.~~

~~30. The method of claim 29, wherein the iodixanol has a concentration of about 5% w/v to about 15% w/v.~~

~~31. The method of claim 29, wherein the iodixanol has a concentration of about 6% w/v to about 13% w/v.~~

~~32. The method of claim 29, wherein the iodixanol has a concentration of about 7% w/v to about 11% w/v.~~

~~33. The method of claim 29, wherein the iodixanol has a concentration of about 8% w/v to about 10% w/v.~~

~~34. The method of any one of the preceding claims, wherein the pretreated suspension comprises sodium benzoate.~~

~~35. The method of claim 34, wherein the sodium benzoate has a concentration of about 0.01 M to about 0.6 M.~~

~~36. The method of claim 34, wherein the sodium benzoate has a concentration of about 0.02 M to about 0.5 M.~~

~~37. The method of claim 34, wherein the sodium benzoate has a concentration of about 0.03 M to about 0.4 M.~~

~~38. The method of claim 34, wherein the sodium benzoate has a concentration of about 0.04 M to about 0.3 M.~~

~~39. The method of claim 34, wherein the sodium benzoate has a concentration of about 0.05 M to about 0.2 M.~~

~~40. The method of any one of the preceding claims, wherein the pretreated suspension further comprises a polyvinyl alcohol (PVA).~~

~~41. The method of claim 40, wherein the PVA has a concentration of about 0.01% w/v to about 0.75% w/v.~~

~~42. The method of any one of the preceding claims, wherein the pretreated suspension further comprises NaCl.~~

~~43. The method of claim 42, wherein the NaCl has a concentration of about 0.005 M to about 0.5 M.~~

~~44. The method of claim 42, wherein the NaCl has a concentration of about 0.01 M to about 0.4 M.~~

~~45. The method of claim 42, wherein the NaCl has a concentration of about 0.015 M to about 0.3 M.~~

~~46. The method of claim 42, wherein the NaCl has a concentration of about 0.015 M to about 0.2 M.~~

~~47. The method of claim 42, wherein the NaCl has a concentration of about 0.015 M to about 0.1 M.~~

~~48. The method of claim 42, wherein the NaCl has a concentration of about 0.02 M to about 0.05 M.~~

~~49. The method of claim 42, wherein the NaCl has a concentration of about .03 M to about 0.07 M.~~

~~50. The method of any one of the preceding claims, wherein the saccharide is sucrose.~~

~~51. The method of claim 50, wherein the sucrose has a concentration of about 8% w/v to about 20% w/v.~~

~~52. The method of claim 50, wherein the sucrose has a concentration of about 7% w/v to about 11% w/v.~~

~~53. The method of claim 50, wherein the sucrose has a concentration of about 8% w/v to about 10% w/v.~~

~~54. The method of claim 50, wherein the sucrose has a concentration of about 16 % w/v to about 20% w/v.~~

55. The method of any one of the preceding claims, wherein the liquid medium or pretreated suspension comprises a buffer.

56. The method of claim 55, wherein the buffer is selected from MOPS, HEPES, TRIS, MES, citrate, and phosphate buffered saline (PBS).

57. The method of claim 56, wherein the buffer is TRIS.

58. The method of any one of claims 55 to 57, wherein the buffer is in a concentration of about 10 mM to about 100 mM.

59. The method of claim 58, wherein the buffer is in a concentration of about 15 mM to about 75 mM.

60. The method of claim 58, wherein the buffer is in a concentration of about 10 mM to about 40 mM.

61. The method of any one of the preceding claims, wherein the liquid medium or the pretreated suspension has a pH of about 7.0 to about 8.5.

62. The method of any one of the preceding claims, further comprising after step (b), aliquoting a predetermined lyophilization volume of the pretreated suspension into individual containers.

63. The method of claim 62, wherein the predetermined lyophilization volume is in the range of about 0.5 mL to about 10.0 mL.

64. The method of claim 62, wherein the predetermined lyophilization volume is in the range of about 1.0 mL to about 3.0 mL.

65. The method of any one of the preceding claims, wherein the pretreated suspension further comprises a poloxamer.

66. The method of claim 65, wherein the poloxamer is Poloxamer 188.

67. The method of claim 65 or claim 66, wherein the poloxamer is in a concentration of about 0.01% w/v to about 0.10% w/v.

68. The method of claim 65 or claim 66, wherein the poloxamer is in a concentration of about 0.02% w/v to about 0.8% w/v.

69. The method of claim 65 or claim 66, wherein the poloxamer is in a concentration of about 0.03% w/v to about 0.7% w/v.

70. The method of claim 65 or claim 66, wherein the poloxamer is in a concentration of about 0.04% w/v to about 0.06% w/v.

71. A product prepared by the process of any one of claims 1 to 70.

~~72. A lyophilized composition comprising lipid nanoparticles encapsulating a nucleic acid, a monosaccharide, and one or more excipients selected from potassium sorbate, thiosulfate, sodium benzoate, and iodixanol.~~

~~73. The lyophilized composition of claim 72, wherein the nucleic acid is an RNA.~~

~~74. The lyophilized composition of claim 73, wherein the RNA is a self-replicating RNA.~~

~~75. The lyophilized composition of claim 73, wherein the RNA is mRNA.~~

~~76. The lyophilized composition of any one of claims 73 to 75, wherein the nucleic acid is from about 20 nucleotides to about 13000 nucleotides in length.~~

~~77. The lyophilized composition of any one of claims 72 to 76, wherein a total lipid to nucleic acid weight ratio in the lyophilized composition is about 50:1 to about 10:1.~~

~~78. The lyophilized composition of claim 77, wherein the total lipid to RNA weight ratio in the lyophilized composition is about 40:1 to about 20:1.~~

~~79. The lyophilized composition of claim 77, wherein the total lipid to RNA weight ratio in the lyophilized composition is about 35:1 to about 25:1.~~

~~80. The lyophilized composition of any one of claims 72 to 79, wherein the lyophilized composition comprises potassium sorbate in a weight ratio of potassium sorbate to RNA of about 30:1 to about 250:1.~~

~~81. The lyophilized composition of any one of claims 72 to 79, wherein the lyophilized composition comprises potassium sorbate in a weight ratio of potassium sorbate to RNA of about 40:1 to about 200:1.~~

~~82. The lyophilized composition of any one of claims 72 to 79, wherein the lyophilized composition comprises potassium sorbate in a weight ratio of potassium sorbate to RNA of about 50:1 to about 175:1.~~

~~83. The lyophilized composition of any one of claims 72 to 82, wherein the lyophilized composition comprises sodium thiosulfate in a weight ratio of sodium thiosulfate to RNA of about 0.25:1 to about 40:1.~~

~~84. The lyophilized composition of any one of claims 72 to 82, wherein the lyophilized composition comprises sodium thiosulfate in a weight ratio of sodium thiosulfate to RNA of about 2:1 to about 10:1.~~

~~85. The lyophilized composition of any one of claims 72 to 82, wherein the lyophilized composition comprises sodium thiosulfate in a weight ratio of sodium thiosulfate to RNA of about 3:1 to about 8:1.~~

~~86. The lyophilized composition of any one of claims 72 to 85, wherein the lyophilized composition comprises sodium benzoate in a weight ratio of sodium benzoate to RNA of about 1:1 to about 12:1.~~

~~87. The lyophilized composition of any one of claims 72 to 85, wherein the lyophilized composition comprises sodium benzoate in a weight ratio of sodium benzoate to RNA of about 2:1 to about 10:1.~~

~~88. The lyophilized composition of any one of claims 72 to 85, wherein the lyophilized composition comprises sodium benzoate in a weight ratio of sodium benzoate to RNA of about 3:1 to about 9:1.~~

~~89. The lyophilized composition of any one of claims 72 to 88, wherein the lyophilized composition comprises iodixanol in a weight ratio of iodixanol to RNA of about 100:1 to about 800:1.~~

~~90. The lyophilized composition of any one of claims 72 to 88, wherein the lyophilized composition comprises iodixanol in a weight ratio of iodixanol to RNA of about 150:1 to about 750:1.~~

~~91. The lyophilized composition of any one of claims 72 to 88, wherein the lyophilized composition comprises iodixanol in a weight ratio of iodixanol to RNA of about 200:1 to about 700:1.~~

~~92. The lyophilized composition of any one of claims 72 to 88, wherein the lyophilized composition comprises iodixanol in a weight ratio of iodixanol to RNA of about 250:1 to about 650:1.~~

~~93. The lyophilized composition of any one of claims 72 to 92, wherein the lyophilized composition further comprises polyvinyl alcohol (PVA) in a weight ratio of PVA to RNA of about 1:1 to about 12:1.~~

~~94. The lyophilized composition of any one of claims 72 to 93, wherein the saccharide is sucrose in a weight ratio of sucrose to RNA of about 100:1 to about 800:1.~~

~~95. The lyophilized composition of any one of claims 72 to 94, wherein the lyophilized composition further comprises a buffer selected from HEPES, MOPS, TRIS, MERS, citrate, and phosphate in a weight ratio of buffer to RNA of about 3:1 to about 150:1.~~

~~96.~~1. A lyophilized composition comprising lipid nanoparticles encapsulating an RNA, poloxamer, potassium sorbate, and a sugar.

~~97.~~2. The composition of claim ~~96~~1, wherein the poloxamer is poloxamer 188.

~~98.~~3. The composition of claim ~~96~~ 1 or claim ~~97~~2, wherein the lyophilized composition comprises about 0.001 to about 1.0 % w/w of the RNA.

~~99. The composition of claim 98, wherein the lyophilized composition comprises about 0.005 to about 0.8 % w/w of the RNA.~~

~~100. The composition of claim 98, wherein the lyophilized composition comprises about 0.01 to about 0.5 % w/w of the RNA.~~

~~101. The composition of claim 98, wherein the lyophilized composition comprises about 0.02 to about 0.4 % w/w of the RNA.~~

~~102. The composition of claim 98, wherein the lyophilized composition comprises about 0.03 to about 0.3 % w/w of the RNA.~~

~~103.~~4. The composition of claim ~~98~~3, wherein the lyophilized composition comprises about 0.04 to about 0.2 % w/w of the RNA.

~~104.~~5. The composition of any one of claims ~~96~~ 1 to ~~103~~4, wherein the lyophilized composition comprises from about 0.5 to about 5.0 % w/w of lipids.

~~105. The composition of claim 104, wherein the lyophilized composition comprises about 1.0 to about 4.0 % w/w lipids.~~

~~106. The composition of claim 104, wherein the lyophilized composition comprises about 1.25 to about 3.0 % w/w lipids.~~

~~107.~~6. The composition of any one of claims ~~96~~ 1 to ~~106~~5, wherein the lyophilized composition comprises about 0.5 to about 2.5 % w/w of tris(hydroxymethyl)aminomethane (TRIS) buffer.

~~108. The composition of claim 107, wherein the lyophilized composition comprises about 0.75 to about 2.25 % w/w of TRIS buffer.~~

~~109. The composition of claim 107, wherein the lyophilized composition comprises about 1.0 to about 2.0 % w/w of TRIS buffer.~~

~~110.~~7. The composition of any one of claims ~~96~~ 1 to ~~109~~6, wherein the lyophilized composition further comprises from about 0.75 to about 2.75 % w/w of NaCl.

~~111. The composition of claim 110, wherein the lyophilized composition comprises about 1.0 to about 2.5 % w/w of NaCl.~~

~~112. The composition of claim 110, wherein the lyophilized composition comprises about 1.25 to about 1.80 % w/w of NaCl.~~

~~113.~~8. The composition of any one of claims ~~96~~ 1 to ~~112~~7, wherein the lyophilized composition comprises from about 85 to about 96 % w/w of the sugar.

~~114. The composition of claim 113, wherein the lyophilized composition comprises about 88 to about 95 % w/w of the sugar.~~

~~115. The composition of claim 113, wherein the lyophilized composition comprises about 90 to about 95 % w/w of the sugar.~~

~~116.~~9. The composition of any one of claims ~~96~~ 1 to ~~115~~8, wherein the sugar is sucrose.

~~117.~~10. The composition of any one of claims ~~96~~ 1 to ~~116~~9, wherein the lyophilized composition comprises about 0.01 to about 1.0 % w/w of the poloxamer.

~~118. The composition of claim 117, wherein the lyophilized composition comprises about 0.02 to about 0.8 % w/w of the poloxamer.~~

~~119. The composition of claim 117, wherein the lyophilized composition comprises about 0.03 to about 0.7 % w/w of the poloxamer.~~

~~120. The composition of claim 117, wherein the lyophilized composition comprises about 0.04 to about 0.6 % w/w of the poloxamer.~~

~~121. The composition of claim 117, wherein the lyophilized composition comprises about 0.05 to about 0.5 % w/w of the poloxamer.~~

~~122. The composition of claim 117, wherein the lyophilized composition comprises about 0.06 to about 0.4 % w/w of the poloxamer.~~

~~123. The composition of claim 117, wherein the lyophilized composition comprises about 0.07 to about 0.3 % w/w of the poloxamer.~~

~~124. The composition of claim 117, wherein the lyophilized composition comprises about 0.09 to about 0.2 % w/w of the poloxamer.~~

~~125.~~11. The composition of any one of claims ~~96~~ 1 to ~~124~~10, wherein the poloxamer is poloxamer 188.

~~126.~~12. The composition of any one of claims ~~96~~ 1 to ~~125~~11, wherein the lyophilized composition comprises from about 0.5 to about 5.0 % w/w of potassium sorbate.

~~127. The composition of claim 126, wherein the lyophilized composition comprises about 0.75 to about 4.0 % w/w of potassium sorbate.~~

~~128. The composition of claim 126, wherein the lyophilized composition comprises about 1.0 to about 3.0 % w/w of potassium sorbate.~~

~~129. The composition of claim 126, wherein the lyophilized composition comprises about 1.25 to about 2.75 % w/w of potassium sorbate.~~

~~130.~~13. A method of preserving a lyophilized composition of any one of claims ~~72~~ 1 to ~~129~~ 12 comprising storing the lyophilized product at a temperature of about 2 °C to about 8 °C.

~~131.~~14. A method of preserving a lyophilized composition of any one of claims ~~72~~ 1 to ~~129~~ 12 comprising storing the lyophilized product at a temperature of about -20 °C.

~~132.~~15. A method of reconstituting a lyophilized composition of any one of claims ~~72~~ 1 to ~~129~~ 12 comprising adding a liquid medium to the lyophilized composition.

~~133.~~16. The method of claim ~~132~~15, wherein the liquid medium is an aqueous medium.

~~134. The method of claim 132 or claim 133, wherein the liquid medium comprises a poloxamer.~~

~~135. The method of claim 134, wherein the poloxamer is P-188.~~

~~136.~~17. The method of ~~any one of claims 132 to 135~~claim 15 or claim 16, wherein the liquid medium further comprises a buffer having a pH of about 7.0 to about 8.5.

~~137.~~18. ~~A method of treating a disease or disorder in a subject comprising administering to the subject~~Use of a lyophilized composition of any one of claims ~~72~~ 1 to ~~129~~ 12 reconstituted in a liquid medium in the preparation of a medicament for the treatment of a disease.

~~138.~~19. The ~~method~~ use of a lyophilized composition of claim ~~137~~18, wherein the reconstituted lyophilized composition is to be administered intravenously, mucosally, or subcutaneously.

~~139.~~20. The ~~method~~ use of a lyophilized composition of claim ~~137~~18, wherein the reconstituted lyophilized composition is to be administered intramuscularly.

~~140.~~21. The ~~method~~ use of a lyophilized composition of claim ~~137~~18, wherein the reconstituted lyophilized composition is to be administered via inhalation.

~~141. The method of claim 137, wherein the reconstituted lyophilized composition is administered mucosally.~~

~~142. The method of claim 137, wherein the reconstituted lyophilized composition is administered subcutaneously.~~