temperature of a spray-dryer ranges between 80ºC to 98ºC. Lipids tend to melt and/or aggregate at the high inlet temperature at or near the spray nozzle. This causes hindrance to the flow of the formulation through the nozzle into the drying chamber, disrupts uniform dispersion of the spray and produces undesirable particle characteristics and poor yield. The present disclosure has unexpectedly solved this problem with the addition of a polymer to the mRNA and lipid nanoparticle mixture before subjecting the mixture to the spray-drying process. As described herein, the inventors observed that adding a polymer to an mRNA and lipid mixture effectively prevents aggregation of lipid nanoparticles and facilitates dry powder formation of fine particles containing mRNA-loaded lipid nanoparticles suitable for inhalation.

[0005] More surprisingly, despite the extremely unstable nature of mRNA, dry powder formulations prepared according to the present disclosure, even under high temperatures and/or high pressures associated with spray-drying, are stable and able to maintain a high degree of mRNA integrity even after long term storage at various temperatures. In addition, a dry powder formulation prepared according to the present disclosure is also characterized with high LNP encapsulation efficiency of mRNA, resulting in high cellular delivery of mRNA. Therefore, the present disclosure fulfils a long-standing need in the mRNA therapy field for a stable dry powder form of mRNA therapeutic, which can easily be stored, transferred, and dispensed. Further, the dry powder formulations of mRNA according to the present disclosure can be administered as dry powder to a patient, e.g. in metered doses or weighed out and reconstituted in single-use amounts, without the need for freezing single-use aliquots of liquid.

[0006] In one aspect, the present disclosure provides a dry powder formulation for delivery of messenger RNA (mRNA) comprising a plurality of spray-dried particles comprising mRNA encoding a protein or a peptide; one or more lipids, and one or more polymers, wherein the mRNA is encapsulated in a lipid nanoparticle (LNPs) and one or more polymers; or wherein the mRNA is encapsulated in a lipid-polymer nanoparticle comprising one or more lipids and one or more polymers. In one ~~aspect~~example, the present disclosure provides a dry powder formulation for delivery of messenger RNA (mRNA) containing a plurality of spray-dried particles comprising mRNA encoding a protein or a peptide, one or more lipids, and one or more polymers.

[0007] In another ~~aspect~~example, the present disclosure provides a dry powder formulation for delivery of messenger RNA (mRNA) containing a plurality of spray-dried particles comprising one or more lipid nanoparticles (LNPs) encapsulating mRNA encoding a peptide or polypeptide, and one or more polymers.

[0008] In still another example~~aspect~~, the present disclosure provides a dry powder formulation for delivery of messenger RNA (mRNA) containing a plurality of spray-dried

particles comprising one or more nanoparticles encapsulating mRNA encoding a peptide or polypeptide, the nanoparticles comprising one or more lipids, and one or more polymers.

[0009] In yet another ~~aspect~~example, the present disclosure provides a dry powder formulation for delivery of cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) containing a plurality of spray-dried particles comprising mRNA encoding a CFTR protein, one or more lipids, and one or more polymers. In some examples, the one or more lipids form one or more lipid nanoparticles (LNPs) encapsulating the mRNA encoding the CFTR protein. In some examples, the one or more lipids and the one or more polymers form one or more nanoparticles encapsulating the mRNA encoding the CFTR protein.

[0009a] ~~In another aspect, the present disclosure provides use of the dry powder formulation as described herein in the manufacture of a pharmaceutical composition for delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression, comprising that the dry powder formulation is to be administered to a subject in need thereof. In another aspect, the present disclosure provides use of the dry powder formulation as described herein in the manufacture of a pharmaceutical composition for delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression, wherein the use comprises reconstituting the dry powder formulation into a liquid solution; and wherein the reconstituted liquid solution is to be administered to a subject in need thereof~~. In yet another aspect, the present disclosure provides a use of the dry powder formulation as described herein in the manufacture of a pharmaceutical composition for delivering mRNA *in vivo* to a subject in need thereof. In yet another aspect, the present disclosure provides a use of the dry powder formulation as described herein in the manufacture of a pharmaceutical composition for treating a disease or disorder in a patient, comprising that an effective dose of mRNA in the dry powder formulation is to be administered to the patient.

[0009b] In a further aspect, the present disclosure provides a dry power formulation manufactured according to a method as described herein. In a further aspect, the present disclosure provides a use of the dry powder formulation as described herein in the manufacture of a pharmaceutical composition for treating a disease or disorder in a patient, comprising that an effective dose of mRNA in the dry powder formulation is to be administered to the patient.

is administered by pulmonary delivery. In some examples, a dry powder formulation is administered by inhalation.

[0042] In a further example, the present disclosure provides a method of delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression comprising steps of: reconstituting a dry powder formulation of described herein into a liquid solution; and administering to a subject in need thereof the reconstituted liquid solution. In some examples, the reconstituted liquid solution is administered by nebulization. In some examples, the subject is suffering from cystic fibrosis.

[0043] In a further aspect, the present disclosure provides a method for manufacturing a dry powder formulation, the method comprising: i. providing a mixture comprising an mRNA, one or more lipids, and one or more polymers; ii. encapsulating the mRNA in a lipid nanoparticle (LNPs) and one or more polymers; or encapsulating the mRNA in a lipid-polymer nanoparticle comprising one or more lipids and one or more polymers; and iii. spray-drying the mixture to form a plurality of particles. In another ~~aspect~~example, the present disclosure provides a method for manufacturing a dry powder formulation including providing a mixture comprising an mRNA, one or more lipids and a polymer; and spray-drying the mixture to form a plurality of particles.

[0044] In some examples, the one or more lipids are first mixed with the mRNA to form mRNA-loaded lipid nanoparticles before adding the polymer.

[0045] In some examples, a method according to the disclosure further includes adding to the mixture one or more excipients prior to spray drying.

[0046] In some examples, the plurality of spray dried particles is characterized by one or more of the following: a) less than 10% moisture content; b) a fraction of fine particles with a volume median diameter less than 5 micrometers; c) Z- average size range of 10- 3000 nm; d) N/P ratio range from 1 to 20; e) mRNA encapsulation efficiency greater than 80%; and f) mRNA integrity greater than 95%.

[0047] In yet another example, the present disclosure provides a method of delivering mRNA *in vivo* comprising administering to a subject in need thereof a dry powder formulation described herein. In some examples, the dry powder formulation is administered via oral, nasal, tracheal, pulmonary or rectal routes. In some examples, the dry powder formulation is administered by inhalation. In some examples, the dry powder formulation is administered by intranasal spray. In some examples, the formulation is administered by a metered-dose inhaler. In some examples, the formulation is administered by a nebulizer.

[0048] In still another example, the present disclosure provides a method of delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression comprising a step of administering to a subject in need thereof a dry powder formulation described herein.

We Claim:

1. A dry powder formulation for delivery of cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) comprising a plurality of spray-dried particles comprising

    mRNA encoding a CFTR protein;

    one or more lipids, and

    one or more polymers.

2. The dry powder formulation of claim 1, wherein the one or more lipids are present in one or more lipid nanoparticles (LNPs) encapsulating the mRNA encoding the CFTR protein.

3. The dry powder formulation of claim 1, wherein the one or more lipids and the one or more polymers are present in one or more lipid nanoparticles (LNPs) encapsulating the mRNA encoding the CFTR protein.

4. The dry powder formulation of any one of the preceding claims, wherein the CFTR mRNA has an integrity of 90% or greater.

5. The dry powder formulation of any one of the preceding claims, wherein the mRNA maintains an integrity of 90% or greater upon storage at or under room temperature for 6 months or longer.

6. The dry powder formulation of any one of the preceding claims, wherein at least 20% of the plurality of spray-dried particles are fine particles.

7. The dry powder formulation of claim 6, wherein the fine particles have a volume median diameter of less than 5 μm.

8. The dry powder formulation of any one of the preceding claims, wherein the dry powder formulation is inhalable.

9. The dry powder formulation of any one of claims 1-7, wherein the formulation is nebulizable upon reconstitution.

10. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers constitute at least 10%, at least 15%, at least 20%, at least 25%, at

least 30%, at least 35%, at least 40%, at least 45%, or at least 50% of the combined weight of the lipids and polymers.

11. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers constitute about 10-90%, 10-80%, 10-70%, 10-60%, 10-50%, 10-40%, 10-30%, 10-20%, 15-20%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, or 15-90% of the combined weight of the lipids and polymers.

12. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers constitute no more than 90%, 80%, 70%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or 20% of the combined weight of the lipids and polymers.

13. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers constitute are selected from a group consisting of chitosan, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(q-caprolactone (PCL), poly amido amines, polyesters, polycarbonates, poly(hydroxyalkyl L-asparagine), poly(hydroxyalkyl L-glutamine), poly(2-alkyloxazoline) acrylates, modified acrylates and polymethacrylate based polymers, poly-N-(2-hydroxyl-propyl)methacrylamide, poly-2-(methacryloyloxy)ethyl phosphorylcholines, poly(2-(methacryloyloxy)ethyl phosphorylcholine), and poly(dimethylaminoethyl methylacrylate) (pDMAEMA).

14. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers comprise a polymethacrylate based polymer.

15. The dry powder formulation of any one of the preceding claims, wherein the one or more polymers comprise Eudragit EPO.

16. The dry powder formulation of any one of claims 2-15, wherein the one or more LNPs encapsulating mRNA have a lipid: mRNA (N/P) ratio ranging from 1 to 20, 1-15, 1-10, 2-8, 2-6, or 2-4.

17. The dry powder formulation of claim 16, wherein the one or more LNPs encapsulating mRNA have a lipid: mRNA (N/P) ratio of 2 or 4.

18. The dry powder formulation of any one of claims 2-17, wherein the LNPs have an encapsulation efficiency of 80% or greater.

19. The dry powder formulation of any one of the preceding claims, wherein the one or more lipids comprise a cationic lipid.

20. The dry powder formulation of claim 19, wherein the cationic lipid is selected from the group consisting of C12-200, DOTAP (1,2-dioleyl-3-trimethytammonium propane), DODAP (1 ,2-dioleyl-3-dimethylammonium propane), DOTMA (1,2-di-O-octadecenyl-3-trimethylammonium propane), DLinDMA, DLin-KC2-DMA, HGT4003, cKK-E12, ICE, and combinations thereof.

21. The dry powder formulation of claim 20, wherein the cationic lipid is cKK-E12.

22. The dry powder formulation of claim 20, wherein the cationic lipid is ICE.

23. The dry powder formulation of any one of claims 19-22, wherein the cationic lipid constitutes about 25-50% of the total lipids in LNPs by molar.

24. The dry powder formulation of any one of the preceding claims, wherein the one or more lipids comprise a PEG-modified lipid.

25. The dry powder formulation of claim 24, wherein the PEG-modified lipid constitutes about 1-15% of the total lipids in LNPs by molar.

26. The dry powder formulation of claim 24, wherein the PEG-modified lipid constitutes at least 1%, 2%, 3%, 4%, 5%, 6%, 8%, 10%, or 12% of the total lipids in LNPs by molar.

27. The dry powder formulation of any one of claims 2-26, wherein the LNPs are two-lipid component LNPs.

28. The dry powder formulation of any one of the preceding claims, wherein the one or more lipids do not comprise a neutral lipid or a cholesterol-based lipid.

29. The dry powder formulation of any one of the preceding claims, wherein the one or more lipids further comprise a neutral lipid or a cholesterol-based lipid.

30. The dry powder formulation of any one of the preceding claims, wherein the one or more lipids further comprise a neutral lipid.

31. The dry powder formulation of claim 29 or 30, wherein the LNPs are three-lipid component LNPs.

32. The dry powder formulation of any one of the preceding claims, further comprising at least one sugar selected from the group consisting of monosaccharides, disaccharides, polysaccharides, glucose, fructose, galactose, mannose, sorbose, lactose, sucrose, cellobiose, trehalose, raffinose, starch, dextran, maltodextrin, cyclodextrins, inulin, xylitol, sorbitol, lactitol, and mannitol.

33. The dry powder formulation of claim 32, wherein the sugar is mannitol.

34. The dry powder formulation of any one of the preceding claims, further comprising a pharmaceutically acceptable excipient selected from the group consisting of esters, urethanes, phosphoesters, phosphazenes, amino acids, collagen, chitosan, polysaccharides, albumin, surfactants, buffers, salts, and combinations thereof.

35. The dry powder formulation of claim 34, wherein the surfactant is selected from the group consisting of CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate), phospholipids, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, sphingomyelins, Octaethylene glycol monododecyl ether, Pentaethylene glycol monododecyl ether, Triton X-100, Cocamide monoethanolamine, Cocamide diethanolamine, Glycerol monostearate, Glycerol monolaurate, Sorbitan moonolaureate, Sorbitan monostearate, Tween 20, Tween 40, Tween 60, Tween 80, Alkyl polyglucosides, and a poloxamer.

36. The dry powder formulation of claim 35, wherein the surfactant is poloxamer.

37. The dry powder formulation of any one of the preceding claims, wherein the CFTR mRNA constitutes about 1-20%, 1-15%, 1-10%, 1-8%, 1-6%, 1-5%, 5-15%, or 5-10% of the total weight of the spray-dried particles.

38. The dry powder formulation of any one of the preceding claims, wherein the CFTR mRNA constitutes about 1%, 2%, 3%, 4%, 5%, 7.5%, 10%, 12.5%, or 15% of the total weight of the spray-dried particles.

39. Use of the dry powder formulation of any one of the preceding claims in the manufacture of a pharmaceutical composition for delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression, comprising that the dry powder formulation is to be administered to a subject in need thereof.

~~40. The use of claim 39, wherein the dry powder formulation is to be administered by pulmonary delivery.~~

~~41. The use of claim 39 or 40, wherein the dry powder formulation is to be administered by inhalation.~~

~~42. Use of the dry powder formulation of any one of claims 1-38 in the manufacture of a pharmaceutical composition for delivering cystic fibrosis conductance regulator (CFTR) messenger RNA (mRNA) for *in vivo* expression, wherein the use comprises reconstituting the dry powder formulation into a liquid solution; and wherein the reconstituted liquid solution is to be administered to a subject in need thereof.~~

~~43. The use of claim 42, wherein the reconstituted liquid solution is to be administered by nebulization.~~

~~44. The use of any one of claims 39-43, wherein the subject is suffering from cystic fibrosis.~~

~~45.~~1. A dry powder formulation for delivery of messenger RNA (mRNA) comprising a plurality of spray-dried particles comprising

mRNA encoding a protein or a peptide;

one or more lipids, and

one or more polymers, wherein the mRNA is encapsulated in a lipid nanoparticle (LNPs) and one or more polymers; or wherein the mRNA is encapsulated in a lipid-polymer nanoparticle comprising one or more lipids and one or more polymers.

~~46.~~2. ~~A~~ The dry powder formulation of claim 1 ~~for delivery of messenger RNA (mRNA) comprising a plurality of spray-dried particles~~ comprising

a. one or more lipid nanoparticles (LNPs) encapsulating mRNA encoding a peptide or polypeptide, and

b. one or more polymers.

~~47.~~3. ~~A~~ The dry powder formulation of claim 1 ~~for delivery of messenger RNA (mRNA) comprising a plurality of spray-dried particles~~ comprising one or more nanoparticles encapsulating mRNA encoding a peptide or polypeptide, the nanoparticles comprising

a. one or more lipids, and

b. one or more polymers.

48.4. The dry powder formulation of any one of claims 451-47, wherein the mRNA has an integrity of 90% or greater.

49.5. The dry powder formulation of any one of claim 1s 45-48, wherein the mRNA maintains an integrity of 90% or greater after storage at or under room temperature for 6 months or longer.

50.6. The dry powder formulation of any one of claim 1s 45-48, wherein the mRNA maintains an integrity of 90% or greater after storage at or under 4°C for 6 months or longer.

51.7. The dry powder formulation of any one of claim 1s 45-50, wherein at least 20% of the plurality of spray-dried particles are fine particles.

52.8. The dry powder formulation of claim 517, wherein the fine particles have a volume median diameter of less than 5 μm.

53.9. The dry powder formulation of any one of claims 1-845-52, wherein the dry powder formulation is inhalable.

54.10. The dry powder formulation of any one of claims 1-845-52, wherein the formulation is nebulizable upon reconstitution.

55.11. The dry powder formulation of any one of claims 46-542-10, wherein the one or more LNPs encapsulating mRNA have a lipid: mRNA (N/P) ratio ranging from 1 to 20, 1-15, 1-10, 2-8, 2-6, or 2-4.

56.12. The dry powder formulation of claim 5511, wherein the one or more LNPs encapsulating mRNA have a lipid: mRNA (N/P) ratio of 2 or 4.

57.13. The dry powder formulation of any one of claims 46-562-12, wherein the mRNA-loaded lipid nanoparticles have an encapsulation efficiency of 80% or greater.

58.14. The dry powder formulation of any one of claims 46-572-13, wherein the one or more mRNA-loaded lipid nanoparticles comprise one or more cationic lipids.

59.15. The dry powder formulation of claim 5814, wherein the one or more cationic lipids are selected from the group consisting of C12-200, DOTAP (1,2-dioleyl-3-trimethytammonium propane), DODAP (1 ,2-dioleyl-3-dimethylammonium propane), DOTMA (1,2-di-O-octadecenyl-3-trimethylammonium propane), DLinDMA, DLin-KC2-DMA, HGT4003, cKK-E12, ICE, and combinations thereof.

~~60.~~16. The dry powder formulation of any one of claims ~~46-59~~2-15, wherein the one or more mRNA-loaded lipid nanoparticles comprise one or more PEG-modified lipids.

~~61.~~17. The dry powder formulation of any one of claims ~~46-60~~2-16, wherein the LNPs are two-lipid component LNPs.

~~62.~~18. The dry powder formulation of any one of claims ~~46-60~~2-16, wherein the one or more mRNA-loaded lipid nanoparticles further comprise one or more neutral lipids or one or more cholesterol-based lipids.

~~63.~~19. The dry powder formulation of claim ~~62~~18, wherein the LNPs are three-lipid component LNPs.

~~64.~~20. The dry powder formulation of any one of claims ~~45-63~~1-19, wherein the one or more polymers constitute less than 20%, 15%, 12%, 10%, 9%, 8%, 7%, 6% or 5% of total weight.

~~65.~~21. The dry powder formulation of any one of claims ~~45-64~~1-20, wherein the one or more polymers constitute at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50% of the combined weight of the lipids and polymers.

~~66.~~22. The dry powder formulation of any one of claims ~~45-65~~1-21, wherein the one or more polymers constitute about 10-90%, 10-80%, 10-70%, 10-60%, 10-50%, 10-40%, 10-30%, 10-20%, 15-20%, 15-25%, 15-30%, 15-35%, 15-40%, 15-45%, 15-50%, 15-55%, 15-60%, 15-65%, 15-70%, 15-75%, 15-80%, or 15-90% of the combined weight of the lipids and polymers.

~~67.~~23. The dry powder formulation of any one of claims ~~45-66~~1-22, wherein the one or more polymers constitute no more than 90%, 80%, 70%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or 20% of the combined weight of the lipids and polymers.

~~68.~~24. The dry powder formulation of any one of claims ~~45-67~~1-23, wherein the one or more polymers are selected from a group consisting chitosan, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(q-caprolactone (PCL), poly amido amines, polyesters, polycarbonates, poly(hydroxyalkyl L-asparagine), poly(hydroxyalkyl L-glutamine), poly(2-alkyloxazoline) acrylates, modified acrylates and polymethacrylate based polymers, poly-N-(2-hydroxyl-propyl)methacrylamide, poly-2-

(methacryloyloxy)ethyl phosphorylcholines, poly(2- (methacryloyloxy)ethyl phosphorylcholine), and poly(dimethylaminoethyl methylacrylate) (pDMAEMA).

~~69.~~25. The dry powder formulation of any one of claims ~~45-68~~1-24, wherein the one or more polymers comprise a polymethacrylate based polymer.

~~70.~~26. The dry powder formulation of any one of claims ~~45-69~~1-25, further comprising at least one sugar selected from the group consisting of monosaccharides, disaccharides, polysaccharides, glucose, fructose, galactose, mannose, sorbose, lactose, sucrose, cellobiose, trehalose, raffinose, starch, dextran, maltodextrin, cyclodextrins, inulin, xylitol, sorbitol, lactitol, and mannitol.

~~71.~~27. The dry powder formulation of claim ~~70~~26, wherein the sugar is mannitol.

~~72.~~28. The dry powder formulation of any one of claims ~~45-71~~1-27, further comprising a pharmaceutically acceptable excipient selected from the group consisting of esters, urethanes, phosphoesters, phosphazenes, amino acids, collagen, chitosan, polysaccharides, albumin, surfactants, buffers, salts, and combination thereof.

~~73.~~29. The dry powder formulation of claim ~~72~~28, wherein the surfactant is selected from the group consisting of CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate), phospholipids, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, sphingomyelins, Octaethylene glycol monododecyl ether, Pentaethylene glycol monododecyl ether, Triton X-100, Cocamide monoethanolamine, Cocamide diethanolamine, Glycerol monostearate, Glycerol monolaurate, Sorbitan moonolaureate, Sorbitan monostearate, Tween 20, Tween 40, Tween 60, Tween 80, Alkyl polyglucosides, a poloxamer and optionally poloxamer 407.

~~74.~~30. The dry powder formulation of claim ~~73~~29, wherein the surfactant is poloxamer.

~~75.~~31. The dry powder formulation of any one of claims ~~45-74~~1-30, wherein the mRNA encodes a peptide.

~~76.~~32. The dry powder formulation of any one of claims ~~45-74~~1-30, wherein the mRNA encodes a therapeutic protein.

~~77.~~33. The dry powder formulation of claim ~~76~~32, wherein the therapeutic protein is CFTR.

~~78.~~34. The dry powder formulation of claim ~~76~~32, wherein the therapeutic protein is OTC.

~~79.~~35. Use of the dry powder formulation of any one of claims ~~45-78~~1-34 in the manufacture of a pharmaceutical composition for delivering mRNA *in vivo* to a subject in need thereof.

~~80.~~36. Use of the dry powder formulation of any one of claims ~~45-78~~1-34 in the manufacture of a pharmaceutical composition for treating a disease or disorder in a patient, comprising that an effective dose of mRNA in the dry powder formulation is to be administered to the patient.

~~81.~~37. The use of claim ~~79~~ 35 or ~~80~~36, wherein the dry powder formulation is to be administered by inhalation.

~~82.~~38. The use of claim ~~79~~ 35 or ~~80~~36, wherein the dry powder formulation is to be administered by intranasal spray.

~~83.~~39. The use of claim ~~79~~ 35 or ~~80~~36, wherein the formulation is to be administered by a metered-dose inhaler.

~~84.~~40. The use of any one of claims ~~80~~36-~~83~~39, wherein the disease or disorder is selected from cystic fibrosis; asthma; COPD; emphysema; primary ciliary dyskinesia (CILD1) with or without situs inversus, or Kartagener syndrome; pulmonary fibrosis; Birt-Hogg-Dube syndrome; hereditary hemorrhagic telangiectasia; alpha-1 antitrypsin deficiency; Cytochrome b positive granulomatous diseases (CGD, X-lined); Cytochrome b positive granulomatous diseases, autosomal recessive; surfactant deficiency diseases, Pulmonary Surfactant Metabolism Dysfunction 1, Pulmonary Surfactant Metabolism Dysfunction 2, Pulmonary Surfactant Metabolism Dysfunction 3; Respiratory distress syndrome of prematurity; tuberculous tuberculosis, lung viral diseases, including influenza, Respiratory Syncytial Virus (RSV).

~~85.~~41. A method for manufacturing a dry powder formulation, the method comprising:

i. providing a mixture comprising an mRNA, one or more lipids, and one or more ~~a~~ polymers;

ii. encapsulating the mRNA in a lipid nanoparticle (LNPs) and one or more polymers; or encapsulating the mRNA in a lipid-polymer nanoparticle comprising one or more lipids and one or more polymers; and

iii. spray-drying the mixture to form a plurality of particles.

~~86.~~42. The method of claim ~~85~~41, wherein the one or more lipids are first mixed with the mRNA to form mRNA-loaded lipid nanoparticles before adding the polymer.

~~87.~~43. The method of claim ~~85~~41, wherein the one or more lipids are mixed with the mRNA and the polymer in a single step to form mRNA-loaded lipid-polymer nanoparticles.

~~88.~~44. The method of any one of claims ~~85-87~~41-43, further comprising adding to the mixture one or more excipients prior to spray drying.

~~89.~~45. The method of any one of claims ~~85-88~~41-44, wherein the plurality of spray dried particles are characterized by one or more of the following:

a) less than 10% moisture content;

b) a fraction of fine particles with a volume median diameter less than 5 μm;

c) Z- average size range of 10- 3000 nm;

d) N/P ratio range from 1 to 20;

e) mRNA encapsulation efficiency of 80% or greater;

f) mRNA integrity of 90% or greater.

~~90.~~46. The method of any one of claims ~~85-89~~41-45, wherein the mRNA encodes a protein or a peptide.

~~91.~~47. The method of any one of claims ~~85-90~~41-46, wherein the mRNA encodes a peptide.

~~92.~~48. The method of any one of claims ~~85-90~~41-46, wherein the mRNA encodes a therapeutic protein.

~~93.~~49. The method of claim ~~92~~48, wherein the therapeutic protein is CFTR.

~~94.~~50. The method of claim ~~92~~48, wherein the therapeutic protein is OTC.

~~95.~~51. A dry power formulation manufactured according to a method of any one of claims ~~85-94~~41-50.

~~96.~~52. Use of the dry powder formulation of claim ~~95-~~51 in the manufacture of a pharmaceutical composition for treating a disease or disorder in a patient, comprising that an effective dose of mRNA in the dry powder formulation is to be administered to the patient.