[00121] Examples of dextrin compounds include hydroxypropyl-sulfobutyl-β-cyclodextrin.

[00122] Examples of dextrin compounds include H107 SIGMA cyclodextrin (Sigma-Aldrich Corp.).

[00123] Examples of dextrin compounds include CAVAMAX, CAVASOL, and CAVITRON cyclodextrins (Ashland Inc.).

[00124] Examples of dextrin compounds include KLEPTOSE and CRYSMEB cyclodextrins (Roquette America Inc.).

[00125] Examples of dextrin compounds include CAPTISOL cyclodextrins (Ligand Pharmaceuticals, Inc.).

[00126] In some embodiments, examples of dextrin compounds include dextrin compounds attached to a polymer chain or network. For example, cyclodextrin molecules can be attached to polymers of polyacrylic acid. In further embodiments, cyclodextrin molecules can be linked together with cross linking compounds such as acryloyl groups. In certain embodiments, vinyl acrylate hydrogel forms with attached cyclodextrin compounds can be used.

[00127] In some aspects, a dextrin compound to be used in a lipid nanoparticle composition of this invention can be combined with an adsorbate compound before being introduced into the lipid nanoparticle composition. Without wishing to be bound by any one particular theory, the pre-adsorption of a sterol compound by the dextrin compound may form an inclusion complex that can prevent a loss of activity of the active agent in the reconstituted drug product.

[00128] Examples of adsorbate compounds include cholesterol, lanosterol, zymosterol, zymostenol, desmosterol, stigmastanol, dihydrolanosterol, 7-dehydrocholesterol.

[00129] Examples of adsorbate compounds include pegylated cholesterols, and cholestane 3-oxo-(C1-22)acyl compounds, for example, cholesteryl acetate, cholesteryl arachidonate, cholesteryl butyrate, cholesteryl hexanoate, cholesteryl myristate, cholesteryl palmitate, cholesteryl behenate, cholesteryl stearate, cholesteryl caprylate,

[00160] Examples of excipients include amino acids such as glycine, alanines, arginine, betaine, leucine, lysine, glutamic acid, aspartic acid, histidine, proline, 4-hydroxyproline, sarcosine, γ-aminobutyric acid, alanopine, octopine, strombine, and trimethylamine N-oxide.

[00161] Examples of excipients include non-ionic surfactants such as polysorbate 20, polysorbate 80, and poloxamer 407.

[00162] Examples of excipients include dispersing agents such as phosphatidyl choline, ethanolamine, acetyltryptophanate, polyethylene glycol, polyvinylpyrrolidone, ethylene glycol, glycerin, glycerol, propylene glycol, sorbitol, xylitol, dextran, and gelatin.

[00163] Examples of excipients include antioxidants such as ascorbic acid, cysteine, thioglycerol, thioglycolic acid, thiosorbitol, and glutathione.

[00164] Examples of excipients include reducing agents such as dithiothreitol, thiols, and thiophenes.

[00165] Examples of excipients include chelating agents such as EDTA, EGTA, glutamic acid, and aspartic acid.

[00166] In some embodiments, the lyophile can be reconstituted using a syringe needle through a stoppered vial. The lyophile can be reconstituted with or without shaking the vial.

[00167] The time for reconstitution can be from 3-30 seconds, or longer.

[00168] In some embodiments, the reconstituted nucleic acid drug product can have less than 0.001% (w/v) of aggregate particles with a size greater than 0.2 μm.

[00169] In certain aspects, the reconstituted nucleic acid drug product can have reduced cytokine activation.

[00170] In additional aspects, the nucleic acid drug product can be reconstituted after a storage time period of six months and retain 80% activity of the nucleic acid agents.

relevant tissues ex vivo, or in vivo through direct dermal application, transdermal application, or injection.

[00179] A inhibitory nucleic acid molecule or composition of this invention may be administered in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the compounds to patients suffering from a disease. Any appropriate route of administration may be employed, for example, administration may be parenteral, intravenous, intraarterial, subcutaneous, intratumoral, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intrahepatic, intracapsular, intrathecal, intracisternal, intraperitoneal, intranasal, aerosol, suppository, or oral administration.

[00180] Compositions and methods of this disclosure can include an expression vector that includes a nucleic acid sequence encoding at least one RNAi molecule of this invention in a manner that allows expression of the nucleic acid molecule.

[00181] The nucleic acid molecules and RNAi molecules of this invention can be expressed from transcription units inserted into DNA or RNA vectors. Recombinant vectors can be DNA plasmids or viral vectors.

[00182] For example, the vector may contain sequences encoding both strands of a RNAi molecule of a duplex, or a single nucleic acid molecule that is self-complementary and thus forms a RNAi molecule. An expression vector may include a nucleic acid sequence encoding two or more nucleic acid molecules.

[00183] A nucleic acid molecule may be expressed within cells from eukaryotic promoters. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector.

[00184] Lipid formulations can be administered to animals by intravenous, intramuscular, or intraperitoneal injection, or orally or by inhalation or other methods as are known in the art.

[00185] Pharmaceutically acceptable formulations for administering oligonucleotides are known and can be used.

[00186] In one embodiment of the above method, the inhibitory nucleic acid molecule is administered at a dosage of about 5 to 500 mg/m^2/day, e.g., 5, 25, 50, 100, 125, 150, 175, 200, 225, 250, 275, or 300 mg/m^2/day.

[00187] In some embodiments, the inhibitory nucleic acid molecules of this invention are administered systemically in dosages from about 1 to 100 mg/kg, e.g., 1, 5, 10, 20, 25, 50, 75, or 100 mg/kg.

[00188] In further embodiments, the dosage can range from about 25 to 500 mg/m^2/day.

[00189] Methods known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" Ed. A. R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, Pa., 2000.

[00190] Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for inhibitory nucleic acid molecules include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[00191] The formulations can be administered to human patients in therapeutically effective amounts (e.g., amounts which prevent, eliminate, or reduce a pathological condition) to provide therapy for a neoplastic disease or condition. The preferred dosage of a nucleotide oligomer of the invention can depend on such variables as the type and extent of the disorder, the overall health status of the particular patient, the formulation of the compound excipients, and its route of administration.

WHAT IS CLAIMED IS:

1. A composition for making a solid lyophile of lipid nanoparticles comprising one or more nucleic acid active agents, the composition comprising:

an aqueous suspension of the lipid nanoparticles in a pharmaceutically acceptable solution, wherein the lipid nanoparticles encapsulate the one or more nucleic acid active agents;

a dextrin compound;

a saccharide sugar compound;

wherein the total amount of the dextrin and sugar compounds is from 2% to 20% (w/v) of the composition;

wherein the dextrin compound is from 40 % to 70% (w/v) of the total amount of the dextrin and sugar compounds; and

wherein upon lyophilization and reconstitution of the composition without filtering, the average size of the nanoparticles is within 5% of their size in the original composition with PDI less than or equal to 0.15.

2. The composition of claim 1, wherein the dextrin compound is from 40 % to 55% (w/v) of the total amount of the dextrin and sugar compounds.

3. The composition of claim 1, wherein the dextrin compound is 40% to 45% (w/v) of the total amount of the dextrin and sugar compounds.

4. The composition of claim 1, wherein upon lyophilization, storage and reconstitution of the composition, the average size of the nanoparticles is within 10% of their size in the original composition.

5. The composition of claim 4, wherein the lyophilized composition is stored at 5°C for at least one month.

6. The composition of claim 4, wherein the lyophilized composition is stored at -20°C for at least one month.

7. The composition of claim 1, wherein the nanoparticles have an average diameter of from 45 nm to 110 nm.

8. The composition of claim 1, wherein the concentration of the nucleic acid active agents is from 1 mg/mL to 10 mg/mL.

9. The composition of claim 1, wherein the lipid nanoparticles comprise a compound selected from compound A6, compound A9, compound AA, compound AB, compound C2, compound F5, compound F7, compound C24, and HEDC.

10. The composition of claim 1, wherein the one or more nucleic acid active agents are RNAi molecules capable of mediating RNA interference.

11. The composition of claim 10, wherein the RNAi molecules are siRNAs, shRNAs, ddRNAs, piRNAs, or rasiRNAs.

12. The composition of claim 1, wherein the one or more nucleic acid active agents are miRNAs, antisense RNAs, plasmids, hybrid oligonucleotides, or aptamers.

13. The composition of claim 1, wherein the pharmaceutically acceptable solution is a HEPES buffer, a phosphate buffer, a citrate buffer, or a buffer containing Tris(hydroxymethyl)aminomethane.

14. The composition of claim 1, wherein the dextrin compound is a cyclodextrin.

15. The composition of claim 14, wherein the cyclodextrin compound has one or more of the 2, 3 and 6 hydroxyl positions substituted with sulfoalkyl, benzenesulfoalkyl, acetoalkyl, hydroxyalkyl, hydroxyalkyl succinate, hydroxyalkyl malonate, hydroxyalkyl glutarate, hydroxyalkyl adipate, hydroxyalkyl, hydroxyalkyl maleate, hydroxyalkyl oxalate, hydroxyalkyl fumarate, hydroxyalkyl citrate, hydroxyalkyl tartrate, hydroxyalkyl malate, or hydroxyalkyl citraconate groups.

16. The composition of claim 14, wherein the cyclodextrin compound is (2-hydroxypropyl)-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin succinate, (2-hydroxypropyl)-γ-cyclodextrin, or 2-hydroxypropyl-γ-cyclodextrin succinate.

17. The composition of claim 14, wherein the cyclodextrin compound is sulfobutyl ether β-cyclodextrin or sulfobutyl ether γ-cyclodextrin.

18. The composition of claim 14, wherein the cyclodextrin compound is methyl-β-cyclodextrin or methyl-γ-cyclodextrin.

19. The composition of claim 14, wherein the cyclodextrin compound is attached to a polymer chain or network.

20. The composition of claim 14, wherein the cyclodextrin compound includes an adsorbate compound.

21. The composition of claim 20, wherein the adsorbate compound is selected from cholesterol, lanosterol, zymosterol, zymostenol, desmosterol, stigmastanol, dihydrolanosterol, 7-dehydrocholesterol, pegylated cholesterol, cholesteryl acetate, cholesteryl arachidonate, cholesteryl butyrate, cholesteryl hexanoate, cholesteryl myristate, cholesteryl palmitate, cholesteryl behenate, cholesteryl stearate, cholesteryl caprylate, cholesteryl n-decanoate, cholesteryl dodecanoate, cholesteryl nervonate, cholesteryl pelargonate, cholesteryl n-valerate, cholesteryl oleate, cholesteryl elaidate, cholesteryl erucate, cholesteryl heptanoate, cholesteryl linolelaidate, cholesteryl linoleate, beta-sitosterol, campesterol, ergosterol, brassicasterol, delta-7-stigmasterol, and delta-7-avenasterol.

22. The composition of claim 1, wherein the saccharide sugar compound is a monosaccharide or disaccharide sugar compound.

23. The composition of claim 22, wherein the sugar compound is selected from sucrose, lactose, lactulose, maltose, trehalose, cellobiose, kojibiose, sakebiose, isomaltose, sophorose, laminaribiose, gentiobiose, turanose, maltulose, isomaltulose, gentiobiulose, mannobiose, melibiose, melibiulose, and xylobiose.

24. A process for making a solid lyophile of one or more nucleic acid active agents, the process comprising lyophilizing a composition according to claim 1.

25. A solid lyophile made by the process of claim 24.

26. A process for making a drug product comprising reconstituting a solid lyophile according to claim 24.

27. A drug product made by the process of claim 26.

28. The composition of claim 1, wherein upon lyophilization and reconstitution of the composition without filtering, the composition has less than 0.001% (w/v) of aggregate particles with a size greater than 0.2 μm.

29. The composition of claim 1, wherein upon lyophilization and reconstitution of the composition after a storage time period of six months, the composition retains at least 80% activity of the nucleic acid agents.