STABILIZATION OF LIPID NANOPARTICLE FORMULATIONS

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of the filing date of U.S. provisional Application Serial Number 63/435,024, entitled "STABILIZATION OF LIPID NANOPARTICLE FORMULATIONS," filed December 23, 2022, the entire contents of which are incorporated by reference herein.

BACKGROUND

Lipid nanoparticle (LNP) formulations are useful drug delivery systems for encapsulating various active pharmaceutical ingredients (APIs), for example, RNAs. LNP formulations commonly include aqueous buffer solutions, for example, phosphate buffer. However, current LNP formulations are susceptible to degradation and aggregate formation during storage at room temperature, thus improvements are needed.

SUMMARY

The disclosure relates to compositions and methods for improving the stability of lipid nanoparticles (LNPs) and one or more active pharmaceutical ingredients (API) encapsulated therein. The disclosure is based, in part, on compositions that directly or indirectly reduce the degradation (e.g., oxidation, hydrolysis, etc.) of one or more lipids components of the lipid nanoparticle. In some examples, the compositions comprise a histidine buffer. In some examples, the histidine buffer inhibits oxidation and/or hydrolysis of one or more lipids of the LNP and/or improves the stability of an API encapsulated within the LNP. The disclosure also provides methods for storing compositions contemplated herein.

Accordingly, in some aspects, the disclosure provides a pharmaceutical composition comprising: (i) a lipid nanoparticle (LNP) comprising one or more ionizable lipids, and (ii) a histidine buffer having a concentration ranging from 5mM to 30 mM histidine and a pH ranging from about 5.0 to about 7.5.

In some examples, the concentration of histidine buffer ranges between 10 mM and 20 mM histidine. In some examples, the concentration of histidine buffer is at least 10 mM. In some examples, the concentration of histidine buffer is 20 mM.

In some examples, the pH of the histidine buffer is about pH 6.0.

In some examples, the histidine buffer further comprises one or more salts. In some examples, the one or more salts comprises NaCl. In some examples, the histidine buffer comprises one or more non-ionic excipients, for example sucrose.

In some examples, the one or more ionizable lipids comprises an unsaturated tail, further optionally wherein the one or more ionizable lipids comprises DLin-MC3-DMA (MC3) and/or Dioleoyl-3-trimethylammonium propane (DOTAP). In some examples, the one or more ionizable lipid consists of MC3 or DOTAP.

In some examples, the LNP comprises one or more nucleic acids. In some examples, the one or more nucleic acids comprises RNA. In some examples, the RNA is mRNA, siRNA, dsRNA, or miRNA. In some examples, the RNA is siRNA.

In some examples, the composition has not been refrigerated or frozen (e.g., after addition of the histidine buffer). In some examples, the composition is stored at a temperature above 4 °C. In some examples, the temperature ranges from about 5 °C to about 30 °C. In some examples, the composition is frozen (e.g., before or after the addition of histidine buffer), and subsequently thawed and stored at a temperature that ranges from about 5 °C to about 30 °C.

In some aspects, the disclosure provides a container containing the pharmaceutical composition as described herein. In some examples, the container is a cartridge, prefilled syringe, or glass vial. In some examples, the container is a prefilled syringe or a glass vial. In some examples, the container is a polymer vial.

In some aspects, the disclosure provides a method for improving chemical stability of a lipid nanoparticle (LNP) pharmaceutical composition, the method comprising: (i) obtaining a non-histidine-buffered LNP pharmaceutical composition comprising a non-histidine buffer; and (ii) performing a buffer exchange procedure to replace the non-histidine buffer with a histidine buffer having a pH between 5.8 and 7.5 to obtain a histidine-buffered LNP pharmaceutical composition.

In some examples, the histidine-buffered LNP pharmaceutical composition comprises one or more ionizable lipids (e.g., one or more ionizable lipids having an unsaturated fatty acid tail). In some examples, the ionizable lipids comprise MC3 and/or DOTAP. In some examples, the ionizable lipids consist of MC3 or DOTAP.

In some examples, the non-histidine buffer comprises a citrate buffer. In some examples, the citrate buffer has a pH ranging from about 3.5 to about 5.5. In some examples, the citrate buffer has a pH of 5.0.

In some examples, the histidine-buffered LNP pharmaceutical composition comprises one or more nucleic acids. In some examples, the one or more nucleic acids comprises RNA. In some examples, the RNA is mRNA, siRNA, dsRNA, or miRNA. In some examples, the RNA is siRNA.

In some examples, the histidine buffer has a pH of 6.0. In some examples, the histidine buffer has a concentration of histidine ranging from about 5 mM to about 30 mM. In some examples, the histidine buffer has a concentration of histidine ranging from about 10 mM and 20 mM. In some examples, the concentration of histidine is at least 10 mM. In some examples, the concentration of histidine is 20 mM.

In some examples, the buffer exchange procedure comprises contacting the non-histidine-buffered LNP pharmaceutical composition to a de-salting column. In some examples, the buffer exchange procedure comprises contacting the non-histidine-buffered LNP pharmaceutical composition to a dialysis tube or performing tangential flow filtration. In some examples, the buffer exchange reaction comprises contacting the non-histidine-buffered LNP pharmaceutical composition to tangential flow filtration.

In some examples, the buffer exchange procedure comprises collecting the histidine-buffered LNP pharmaceutical composition in a container (e.g., a vial or syringe). In some examples, the container is a cartridge, prefilled syringe, or glass vial. In some examples, the vial is a glass vial. In some examples, the vial is a polymer vial.

In some examples, the method further comprises storing the histidine-buffered LNP pharmaceutical composition at a temperature above 4 °C. In some examples, the temperature ranges from about 5 °C to about 30 °C.

In some examples, the histidine-buffered LNP pharmaceutical composition comprises fewer hydrolyzed lipids relative to a non-histidine-buffered LNP pharmaceutical composition stored in a phosphate buffer.

In some examples, the histidine-buffered LNP pharmaceutical composition comprises fewer oxidized lipids relative to a non-histidine-buffered LNP pharmaceutical composition stored in a phosphate buffer.

In some examples, the histidine-buffered LNP pharmaceutical composition comprises LNPs having increased colloidal stability relative to non-histidine-buffered LNPs stored in a pharmaceutical composition comprising phosphate buffer.

In some aspects, the disclosure provides a method for preparing a lipid nanoparticle (LNP) pharmaceutical composition, the method comprising (i) preparing a first lipid composition comprising one or more lipids; (ii) preparing a second lipid composition comprising a siRNA and an ionizable lipid, and (iii) mixing the first lipid composition and the second lipid composition, wherein the first lipid composition and second lipid composition are prepared using a histidine buffer having a pH between 5.8 and 6.5 and a histidine concentration of between 5 mM to 30 mM.

In some aspects, the disclosure provides a method for preparing a lipid nanoparticle (LNP) pharmaceutical composition, the method comprising: (i) obtaining a lipid composition comprising a siRNA and an ionizable lipid, and; (ii) mixing the lipid composition with a histidine buffer having a pH between 5.8 and 6.5 and a histidine concentration of between 5mM to 30 mM.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows representative structural features of two ionizable lipids, MC3 and DOTAP, used to manufacture lipid nanoparticles (LNPs).

FIGs. 2A and 2B show the percentage of DOTAP (FIG. 2A) and MC3 (FIG. 2B) lipids, respectively, that are intact over a period of four weeks following storage in either glass (BT5933) or cyclic olefin polymer (COP) vials at different temperatures. Briefly, DOTAP or MC3 was dissolved in ethanol at 4 mg/mL concentration. Then, the solution was diluted in 1X PBS buffer and filled into either glass vials or COP vials.

FIGs. 3A-3C show representative data indicating percentage hydrolysis (FIG. 3A) and percentage oxidation (FIG. 3B) of DOTAP lipids, and percentage hydrolysis (FIG. 3C) of MC3 lipids over a period of four weeks following storage in either glass (BT5933) or cyclic olefin polymer (COP) vials at different temperatures.

FIGs. 4A and 4B show representative data indicating storage of DOTAP lipids in histidine buffers improves the percentage of intact DOTAP lipids after storage across a range of temperatures over four weeks (FIG. 4A) and that histidine buffers reduce hydrolysis of DOTAP