[0005] Accordingly, a need exists for nanoparticle therapeutics and methods of making such nanoparticles that are capable of delivering therapeutic levels of drug to treat diseases such as cancer, while also reducing patient side effects.

SUMMARY

[0005a] In a first aspect of the present disclosure, there is provided a method of preparing a plurality of therapeutic nanoparticles, comprising:

combining a therapeutic agent, a first polymer, and a halogenated carboxylic acid that is an aliphatic charboxylic acid with an organic solvent to form a first organic phase, wherein the solids used to form the first organic phase comprise 1 to 50% weight of the first organic phase, wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, and wherein the halogenated carboxylic acid has a pK_a of less than 3.5 at 25°C;

combining the first organic phase with a first aqueous solution to form the plurality of therapeutic nanoparticles; and

recovering the therapeutic nanoparticles by filtration.

[0005b] In a second aspect of the present disclosure, there is provided a method of preparing a plurality of therapeutic nanoparticles, comprising:

combining a therapeutic agent, a first polymer, and a halogenated carboxylic acid that is an aliphatic carboxylic acid, with an organic solvent to form a first organic phase, wherein the solids used to form the first organic phase comprise 1 to 50% weight of the first organic phase, wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, and wherein the halogenated carboxylic acid has a pK_a of less than 3.5 at 25°C;

combining the first organic phase with a first aqueous solution to form a second phase;

emulsifying the second phase to form an emulsion phase;

quenching the emulsion phase to form a quenched phase; and

filtering the quenched phase to recover the therapeutic nanoparticles.

[0005c] In a third aspect of the present disclosure, there is provided a therapeutic nanoparticle comprising:

0.2 to 35 weight percent of a Bcr-Abl tyrosine-kinase inhibitor selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof;

50 to 99.8 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises about 10 to

properties of the resultant therapeutic nanoparticles. As discussed above, in some embodiments, use of an acid in a disclosed process may confer advantageous properties to therapeutic nanoparticles prepared by the process, such as, *e.g.*, improved drug loading and/or controlled release properties. Without wishing to be bound by any theory, it is believed that the acid confers advantageous properties to disclosed nanoparticles by improving the solubility of the therapeutic agent in solvents used in the preparation of the therapeutic nanoparticles.

[0070] Any suitable acid may be used in a nanoparticle preparation process. In some embodiments, the acid may be an organic acid. For example, a contemplated acid may be a carboxylic acid (*e.g.*, a monocarboxylic acid, dicarboxylic acid, tricarboxylic acid, or the like), a sulfinic acid, a sulfenic acid, or a sulfonic acid. In some cases, a contemplated acid may include a mixture of two or more acids. For example, in some embodiments, a contemplated acid may comprise a mixture of two acids, in some embodiments a mixture of three acids, in some embodiments a mixture of four acids, or in some embodiments a mixture of five acids. In certain embodiments, an ester of an acid may be used. In some cases, a salt of an acid may be used. In some embodiments, the acid may be an inorganic acid. Exemplary inorganic acids include hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, boric acid, hydrofluoric acid, and hydrobromic acid.

[0071] For example, a disclosed carboxylic acid may be an aliphatic carboxylic acid (*i.e.*, a carboxylic acid having acyclic, branched or unbranched, hydrocarbon chain). Disclosed carboxylic acids may, in some embodiments, be substituted with one or more functional groups including, but not limited to, halogen (*i.e.*, F, Cl, Br, and I), sulfonyl, nitro, and oxo. For example, the carboxylic acid may be a halogenated carboxylic acid (*e.g.*, trifluoroacetic acid). In certain embodiments, a disclosed carboxylic acid may be unsubstituted.

[0072] Exemplary carboxylic acids may include a substituted or unsubstituted fatty acid (*e.g.*, C_8-C_{50} fatty acid). In some instances, the fatty acid may be a C_{10}-C_{20} fatty acid. In other instances, the fatty acid may be a C_{15}-C_{20} fatty acid. The fatty acid may, in some cases, be saturated. In other embodiments, the fatty acid may be unsaturated. For instance, the fatty acid may be a monounsaturated fatty acid or a polyunsaturated fatty acid. In some embodiments, a double bond of an unsaturated fatty acid group can be in the *cis* conformation. In some embodiments, a double bond of an unsaturated fatty acid can be in the *trans* conformation.

[0073] Non-limiting examples of carboxylic acids include formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, heptanoic acid, caprylic acid, nonanoic

CLAIMS

1. A method of preparing a plurality of therapeutic nanoparticles, comprising:

combining a therapeutic agent, a first polymer, and a halogenated carboxylic acid that is an aliphatic carboxylic acid with an organic solvent to form a first organic phase, wherein the solids used to form the first organic phase comprise 1 to 50% weight of the first organic phase, wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, and wherein the halogenated carboxylic acid has a pK_a of less than 3.5 at 25 °C;

combining the first organic phase with a first aqueous solution to form the plurality of therapeutic nanoparticles; and

recovering the therapeutic nanoparticles by filtration.

2. The method of claim 1, wherein the halogenated carboxylic acid has a pK_a of less than 2.0 at 25 °C.

3. The method of claim 1 or 2, wherein the therapeutic nanoparticles comprise 0.2 to 35 weight percent of the therapeutic agent.

4. The method of any one of claims 1-3, wherein the therapeutic nanoparticles prepared by the method have a therapeutic agent loading at least 2 times higher as compared to therapeutic nanoparticles prepared by another method, wherein the other method is identical to the method except that the other method does not include the halogenated carboxylic acid.

9. A method of preparing a plurality of therapeutic nanoparticles, comprising:

combining a therapeutic agent, a first polymer, and a halogenated carboxylic acid that is an aliphatic carboxylic acid, with an organic solvent to form a first organic phase, wherein the solids used to form the first organic phase comprise 1 to 50% weight of the first organic phase, wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, and wherein the halogenated carboxylic acid has a pK_a of less than 3.5 at 25 °C;

combining the first organic phase with a first aqueous solution to form a second phase;

emulsifying the second phase to form an emulsion phase;

quenching the emulsion phase to form a quenched phase; and

filtering the quenched phase to recover the therapeutic nanoparticles.

10. A therapeutic nanoparticle comprising:

0.2 to 35 weight percent of a Bcr-Abl tyrosine-kinase inhibitor selected from imatinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof;

50 to 99.8 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic)-co-poly(glycolic) acid-