[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, and wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer;

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, and wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer;

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;

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

about 30 weight percent poly(ethylene)glycol; and

an organic acid having a pK_a of less than about 3.5 at 25 °C wherein the organic acid is a halogenated carboxylic acid that is an aliphatic carboxylic acid.

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

0.5 to 35 weight percent of dasatinib or a pharmaceutically acceptable salt thereof;

30 to 99.5 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer; and

0.0001 to 0.5 weight percent of an organic acid having a pK_a of less than 3.5 at 25 °C, wherein the organic acid is a halogenated carboxylic acid that is an aliphatic carboxylic acid, and wherein the therapeutic nanoparticle comprises 10 to 25 weight percent poly(ethylene)glycol.

[0005e] In a fifth aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles as disclosed herein and a pharmaceutically acceptable excipient.

[0005f] In a sixth aspect of the present disclosure, there is provided a use of a composition comprising the therapeutic nanoparticle as disclosed herein in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0005g] In a seventh aspect of the present disclosure, there is provided a composition comprising the therapeutic nanoparticle as disclosed herein for use in treating cancer in a patient in need thereof.

[0006] Described herein is a process for preparing therapeutic nanoparticles, where the process includes combining a therapeutic agent with an organic acid.

[0007] A method of preparing a plurality of therapeutic nanoparticles is provided. The method comprises combining a therapeutic agent, a first polymer, and an organic acid with an organic solvent to form a first organic phase having about 1 to about 50%

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, and wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer;

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 3.5 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.

5. The method of any one of claims 1-4, wherein the therapeutic agent has a solubility in a first solution consisting of the therapeutic agent, the organic solvent, and the halogenated carboxylic acid that is at least 5 times higher as compared to a second solution consisting of the therapeutic agent and the organic solvent.

6. The method of claim 5, wherein the concentration of the halogenated carboxylic acid is at least 1 weight percent.

7. The method of any one of claims 1-6, wherein the halogenated carboxylic acid has a pKa of less than 1.0 at 25°C.

8. The method of claim 7, wherein the halogenated carboxylic acid is trifluoroacetic 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, and wherein the first polymer comprises poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer;

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;

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 about 30 weight percent poly(ethylene)glycol; and

an organic acid having a pK_a of less than about 3.5 at 25 °C wherein the organic acid is a halogenated carboxylic acid that is an aliphatic carboxylic acid.

11. A therapeutic nanoparticle comprising:

0.5 to 35 weight percent of dasatinib or a pharmaceutically acceptable salt thereof;

30 to 99.5 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer; and

0.0001 to 0.5 weight percent of an organic acid having a pK_a of less than 3.5 at 25 °C, wherein the organic acid is a halogenated carboxylic acid that is an aliphatic carboxylic acid, and wherein the therapeutic nanoparticle comprises 10 to 25 weight percent poly(ethylene)glycol.

12. The therapeutic nanoparticle of any one of claims 10-11, wherein the organic acid is trifluoroacetic acid.

13. A pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles of any of claims 10-12 and a pharmaceutically acceptable excipient.

14. Use of a composition comprising the therapeutic nanoparticle of any one of claims 10-12 in the manufacture of a medicament for treating cancer in a patient in need thereof.

15. The use of claim 14, wherein the cancer is selected from the group consisting of chronic myelomonocytic leukemia, hypereosinophilic syndrome, renal cell carcinoma, hepatocellular carcinoma, Philadelphia chromosome positive acute lymphoblastic leukemia, non-small cell lung cancer, pancreatic cancer, breast cancer, a solid tumor, gastrointestinal stromal tumor, and mantle cell lymphoma.

16. A composition comprising the therapeutic nanoparticle of any one of claims 10-12 for use in treating cancer in a patient in need thereof.