[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 an organic acid with an organic solvent to form a first organic phase having about 1 to about 50% solids;

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 an organic acid, with an organic solvent to form a first organic phase having about 1 to about 50% solids;

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 solubilized phase to recover the therapeutic nanoparticles.

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

emulsification of a first organic phase comprising a first polymer, a therapeutic agent, and an organic acid thereby forming an emulsion phase;

quenching of the emulsion phase thereby forming a quenched phase; and

filtration of the quenched phase to recover the therapeutic nanoparticles.

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

about 0.2 to about 35 weight percent of a Bcr-Abl tyrosine-kinase inhibitor; and

about 50 to about 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.

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

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

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

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

[0005f] In a sixth aspect of the present disclosure, there is provided a therapeutic nanoparticle prepared by:

emulsification of a first organic phase comprising a first polymer, a Bcr-Abl tyrosine-kinase inhibitor, and an organic acid having a pK_a of less than about 3.5 at 25 °C thereby forming an emulsion phase;

quenching of the emulsion phase thereby forming a quenched phase; and

filtration of the quenched phase to recover the therapeutic nanoparticles.

[0005g] In a seventh 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.

[0005h] In an eighth 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.

[0005i] In a ninth 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] ~~In one aspect, a~~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%

solids, combining the first organic phase with a first aqueous solution to form the plurality of therapeutic nanoparticles, and recovering the therapeutic nanoparticles by filtration.

In some embodiments, the organic acid may have a pK_a of less than about 3.5 at 25 °C. In other embodiments, the organic acid may have a pK_a of less than about 2.0 at 25 °C.In still other embodiments, the organic acid may have a pK_a of less than about 1 at 25 °C. In further embodiments, the organic acid may have a pK_a of less than about 0 at 25 °C.

[0008] In some cases, the organic acid may have a boiling point of between about 50 °C and about 110 °C. In some embodiments, the organic acid may have a melting point of between about -30 °C and about 0 °C.

[0009] In some instances, the therapeutic nanoparticles may comprise about 0.2 to about 35 weight percent of the therapeutic agent. In other instances, the therapeutic nanoparticles may comprise about 1 to about 10 weight percent of the therapeutic agent.

[0010] In some embodiments, the method may be a first method and the therapeutic nanoparticles may have a therapeutic agent loading at least about 2 times higher as compared to therapeutic nanoparticles prepared by a second method, wherein the second method is identical to the first method except that the second method does not include the organic acid. In some cases, the therapeutic nanoparticles may have a therapeutic agent loading at least about 5 times higher. In other cases, the therapeutic nanoparticles may have a therapeutic agent loading at least about 10 times higher.

[0011] In some cases, the therapeutic agent may have a solubility in a first solution consisting of the therapeutic agent, the organic solvent, and the organic acid that is at least 5 times higher as compared to a second solution consisting of the therapeutic agent and the

[0031] A~~In yet another aspect, a~~ therapeutic nanoparticle is provided. The therapeutic nanoparticle is prepared by emulsification of a first organic phase comprising a first polymer, a therapeutic agent, and an organic acid thereby forming an emulsion phase, quenching of the emulsion phase thereby forming a quenched phase, and filtration of the quenched phase to recover the therapeutic nanoparticles.

[0032] A~~In still another aspect, a~~ therapeutic nanoparticle is provided. The therapeutic nanoparticle comprises about 0.2 to about 35 weight percent of a Bcr-Abl tyrosine-kinase inhibitor, and about 50 to about 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.

[0033] In some embodiments, the therapeutic nanoparticle may further comprise an organic acid having a pK_a of less than about 3.5 at 25 °C. In another embodiment, the organic acid may have a pK_a of between about -1 and about 2 at 25 °C.

[0034] In some cases, the organic acid may be trifluoroacetic acid.

[0035] In some embodiments, the hydrodynamic diameter of the therapeutic nanoparticle may be about 60 to about 150 nm. In another embodiment, the hydrodynamic diameter of the therapeutic nanoparticle may be about 90 to about 140 nm.

[0036] In some instances, the therapeutic nanoparticle may comprise about 1 to about 10 weight percent of the Bcr-Abl tyrosine-kinase inhibitor. In other instances, the therapeutic nanoparticle may comprise about 2 to about 5 weight percent of the Bcr-Abl tyrosine-kinase inhibitor.

[0037] In some embodiments, the therapeutic nanoparticle may substantially retain the Bcr-Abl tyrosine-kinase inhibitor for at least 1 minute when placed in a phosphate buffer solution at 37 °C. In other embodiments, the therapeutic nanoparticle may substantially immediately release less than about 5% of the Bcr-Abl tyrosine-kinase inhibitor when placed in a phosphate buffer solution at 37 °C. In further embodiments, the therapeutic nanoparticle may release about 0.01 to about 25% of the Bcr-Abl tyrosine-kinase inhibitor over about 1 hour when placed in a phosphate buffer solution at 37 °C. In still other embodiments, the therapeutic nanoparticle may release about 10 to about 45% of the Bcr-Abl tyrosine-kinase inhibitor over about 4 hours when placed in a phosphate buffer solution at 37 °C.

[0038] In some cases, the Bcr-Abl tyrosine-kinase inhibitor may be dasatinib or a pharmaceutically acceptable salt thereof. In other cases, the Bcr-Abl tyrosine-kinase inhibitor may be selected from the group consisting of imatinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof.

[0039] In some embodiments, the therapeutic nanoparticle the poly(lactic) acid-poly(ethylene)glycol copolymer may have a poly(lactic) acid number average molecular weight fraction of about 0.6 to about 0.95, about 0.6 to about 0.8, about 0.75 to about 0.85, or about 0.7 to about 0.9.

[0040] In certain embodiments, the therapeutic nanoparticle may comprise about 10 to about 25 weight percent poly(ethylene)glycol, about 10 to about 20 weight percent poly(ethylene)glycol, about 15 to about 25 weight percent poly(ethylene)glycol, or about 20 to about 30 weight percent poly(ethylene)glycol.

[0041] In some cases, the therapeutic nanoparticle may further comprise about 0.2 to about 30 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand. In some embodiments, the therapeutic nanoparticle may further comprise about 0.2 to about 30 weight percent poly(lactic) acid-co-poly(glycolic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand. The targeting ligand may be covalently bound to the poly(ethylene)glycol.

[0042] A~~In another aspect, a~~ therapeutic nanoparticle is provided. The therapeutic nanoparticle comprises about 0.5 to about 35 weight percent of dasatinib or a pharmaceutically acceptable salt thereof, about 30 to about 99.5 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer or poly(lactic)-co-poly(glycolic) acid-poly(ethylene)glycol copolymer, and optionally about 0.0001 to about 0.5 weight percent of an organic acid having a pK_a of less than about 3.5 at 25 °C, wherein the therapeutic nanoparticle comprises about 10 to about 25 weight percent poly(ethylene)glycol.

[0043] In certain embodiments, a contemplated therapeutic nanoparticle further comprises a mixture of two or more organic acids. For example, in some embodiments, a contemplated therapeutic nanoparticle comprises a mixture of two organic acids, a mixture of three organic acids, a mixture of four organic acids, or a mixture of five organic acids.

[0044] A~~In yet another aspect, a~~ therapeutic nanoparticle is provided. The therapeutic nanoparticle is prepared by emulsification of a first organic phase comprising a first polymer, a Bcr-Abl tyrosine-kinase inhibitor, and an organic acid having a pK_a of less than about 3.5 at

25 °C thereby forming an emulsion phase, quenching of the emulsion phase thereby forming a quenched phase, and filtration of the quenched phase to recover the therapeutic nanoparticles.

[0045] ~~In still another aspect, a~~ A pharmaceutically acceptable composition is provided. The pharmaceutically acceptable composition may comprise a plurality of therapeutic nanoparticles as described herein and a pharmaceutically acceptable excipient.

[0046] In some embodiments, the pharmaceutically acceptable composition may further comprise a saccharide. In some instances, the saccharide may be a disaccharide selected from the group consisting of sucrose or trehalose, or a mixture thereof. In another embodiment, the pharmaceutically acceptable composition may further comprise a cyclodextrin. In some cases, the cyclodextrin may be selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, and mixtures thereof.

[0047] ~~In yet another aspect, a~~ A method of treating cancer in a patient in need thereof is provided. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a therapeutic nanoparticle as described herein. In some embodiments, the cancer may be chronic myelogenous leukemia. In other embodiments, the cancer may be 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, and mantle cell lymphoma.

[0048] ~~In still another aspect, a~~ A method of treating a gastrointestinal stromal tumor in a patient in need thereof is provided. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a therapeutic nanoparticle as described herein.

[0049] ~~In another aspect, t~~ There is provided a therapeutic nanoparticle as described herein for use as a medicament in a warm-blooded animal such as man.

[0050] ~~In yet another aspect, t~~ There is provided a therapeutic nanoparticle as described herein for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

[0051] ~~In still another aspect, t~~ There is provided a therapeutic nanoparticle as described herein for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of solid tumor disease.

[0052] ~~In yet another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein in the prevention or treatment of cancer in a warm blooded animal such as man.

[0053] ~~In still another aspect, t~~There is provided a therapeutic nanoparticle as described herein for use in the prevention or treatment of cancer in a warm blooded animal such as man.

[0054] ~~In yet another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein in the manufacture of a medicament for the prevention or treatment of cancer in a warm blooded animal such as man.

[0055] ~~In still another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein for the production of an anti-proliferative effect in a warm-blooded animal such as man.

[0056] ~~In yet another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

[0057] ~~In still another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein in the manufacture of a medicament for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of solid tumor disease.

[0058] ~~In yet another aspect, t~~There is provided a method for producing an anti-proliferative effect in a warm blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a therapeutic nanoparticle as described herein.

[0059] ~~In still another aspect, t~~There is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumor disease in a warm blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a therapeutic nanoparticle as described herein.

[0060] ~~In yet another aspect, t~~There is provided a therapeutic nanoparticle as described herein for use in the prevention or treatment of solid tumor disease in a warm blooded animal such as man.

[0061] ~~In still another aspect, t~~There is provided the use of a therapeutic nanoparticle as described herein in the manufacture of a medicament for use in the prevention or treatment of solid tumor disease in a warm blooded animal such as man.

[0062] ~~In yet another aspect, t~~There is provided a method for the prevention or treatment of solid tumor disease in a warm blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a therapeutic nanoparticle as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0063] Figure 1 depicts a pictorial representation of one embodiment of a disclosed nanoparticle.

[0064] Figure 2 is flow chart for an emulsion process for forming a disclosed nanoparticle.

[0065] Figure 3A is a flow diagram for a disclosed emulsion process.

[0066] Figure 3B is a flow diagram for a disclosed emulsion process.

[0067] Figure 4 depicts *in vitro* release profiles for various nanoparticle formulations.

DETAILED DESCRIPTION

[0068] Described herein is a process for preparing therapeutic nanoparticles, where the process includes combining a therapeutic agent with an organic acid. In some embodiments, inclusion of an organic acid in a nanoparticle preparation process may result in nanoparticles containing a substantially high loading of a therapeutic agent. Furthermore, in certain embodiments, nanoparticles that include or are prepared in the presence of the organic acid may exhibit improved controlled release properties. For example, the disclosed nanoparticles may more slowly release the therapeutic agent as compared to nanoparticles prepared in the absence of the organic acid. Also described herein are therapeutic nanoparticles prepared by the disclosed process.

[0069] As one of ordinary skill in the art will appreciate, nanoparticle formulations of some therapeutic agents prove more problematic than for other therapeutic agents. For example, attempting to prepare nanoparticles containing a problematic therapeutic agent can result in nanoparticles with insufficient drug loading, poorly controlled release properties, particles that are too large, *etc.* Surprisingly, it has been discovered that including an acid (*e.g.*, trifluoroacetic acid) in a process for preparing therapeutic nanoparticles can improve the

109. The pharmaceutically acceptable composition of claim 107, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, and mixtures thereof.

110. Use of a composition comprising the therapeutic nanoparticle of any one of claims 66-104 in the manufacture of a medicament for ~~A method of~~ treating cancer in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a composition comprising the therapeutic nanoparticle of any one of claims 66-104~~.

111. The ~~method~~ use of claim 110, wherein the cancer is chronic myelogenous leukemia.

112. The ~~method~~ use of claim 110, 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.

113. A composition comprising the therapeutic nanoparticle of any one of claims 66-104 for use in treating cancer in a patient in need thereof.