[0005] Therapeutic agents containing at least one basic nitrogen atom (*i.e.*, protonatable nitrogen-containing therapeutic agents) represent an important group of therapeutic agents. However, nanoparticle formulations of this class of drugs are often hindered by undesirable properties, *e.g.*, burst release profiles and poor drug loading.

[0006] Accordingly, a need exists for nanoparticle therapeutics and methods of making such nanoparticles that are capable of delivering therapeutic levels of protonatable nitrogen-containing therapeutic agents to treat diseases such as cancer, while also reducing patient side effects.

SUMMARY

[0006a] In a first aspect of the present disclosure, there is provided a therapeutic nanoparticle comprising:

about 0.05 to about 30 weight percent of a substantially hydrophobic acid;

about 0.2 to about 20 weight percent of a basic therapeutic agent having a protonatable nitrogen; wherein the pK_a of the basic therapeutic agent is at least about 1.0 pK_a units greater than the pK_a of the hydrophobic acid; and

about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic acid-co-glycolic acid)-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises about 10 to about 30 weight percent poly(ethylene)glycol.

[0006b] In a second aspect of the present disclosure, there is provided a therapeutic nanoparticle comprising:

a substantially hydrophobic acid, wherein the molar ratio of the substantially hydrophobic acid to the basic therapeutic agent is about 0.25:1 to about 2:1;

about 0.2 to about 20 weight percent of a basic therapeutic agent having a protonatable nitrogen; wherein the pKa of the basic therapeutic agent is at least about 1.0 pK_a units greater than the pK_a of the hydrophobic acid; and

about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic acid-co-glycolic acid)-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises about 10 to about 30 weight percent poly(ethylene)glycol.

{0006c} In a third aspect of the present disclosure, there is provided a therapeutic nanoparticle comprising:

a hydrophobic ion-pair comprising a hydrophobic acid and a therapeutic agent having at least one ionizable amine moiety; wherein difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least about 1.0 pKa units; and

about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of about 15 kDa to about 20 kDa poly(lactic acid) and a number average molecular weight of about 4 kDa to about 6 kDa poly(ethylene)glycol.

{0006d} In a fourth aspect of the present disclosure, there is provided a therapeutic nanoparticle prepared by:

emulsification of a first organic phase comprising a first polymer, a basic therapeutic agent having a protonatable nitrogen, and a substantially hydrophobic 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.

{0006e} 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.

{0006f} 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.

{0006g} In a seventh 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 a gastrointestinal stromal tumor in a patient in need thereof.

{0006h} In an eigth aspect of the present disclosure, there is provided a process for preparing a therapeutic nanoparticle, comprising:

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

emulsifying the second phase to form an emulsion phase, wherein the emulsion phase comprises a first polymer, a basic therapeutic agent having a protonatable nitrogen, and a substantially hydrophobic acid;

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

filtering the quenched phase to recover the therapeutic nanoparticles.

[0006i] 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.

[0006j] In a tenth aspect of the present disclosure, there is provided A composition comprising the therapeutic nanoparticle as disclosed herein for use in treating a gastrointestinal stromal tumor in a patient in need thereof.

[0007] Described herein are polymeric nanoparticles that include a protonatable nitrogen-containing therapeutic agent, and methods of making and using such therapeutic nanoparticles.

[0008] ~~In one aspect, a~~A therapeutic nanoparticle is provided. The therapeutic nanoparticle comprises about 0.05 to about 30 weight percent of a substantially hydrophobic acid, about 0.2 to about 20 weight percent of a basic therapeutic agent having a protonatable nitrogen, wherein the pK_a of the basic therapeutic agent is at least about 1.0 pK_a units greater than the pK_a of the hydrophobic acid, and about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic acid-co-glycolic acid)-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises about 10 to about 30 weight percent poly(ethylene)glycol.

[0009] A~~In another aspect, a~~ therapeutic nanoparticle is provided. The therapeutic nanoparticle comprises a substantially hydrophobic acid, wherein the molar ratio of the substantially hydrophobic acid to the basic therapeutic agent is about 0.25:1 to about 2:1, about 0.2 to about 20 weight percent of a basic therapeutic agent having a protonatable nitrogen, wherein the pKa of the basic therapeutic agent is at least about 1.0 pK_a units greater than the pK_a of the hydrophobic acid, and about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer or a diblock poly(lactic acid-co-glycolic acid)-poly(ethylene)glycol copolymer, wherein the therapeutic nanoparticle comprises about 10 to about 30 weight percent poly(ethylene)glycol.

[0010] In some embodiments, the molar ratio of the substantially hydrophobic acid to the basic therapeutic agent is about 0.5:1 to about 1.5:1. In certain embodiments, the molar

ratio of the substantially hydrophobic acid to the basic therapeutic agent is about 0.75:1 to about 1.25:1.

[0011] In certain embodiments, the pK_a of the basic therapeutic agent is at least about 2.0 pK_a units greater than the pK_a of the hydrophobic acid. In other embodiments, the pK_a of the basic therapeutic agent is at least about 4.0 pK_a units greater than the pK_a of the hydrophobic acid.

[0012] ~~In another aspect, a~~A therapeutic nanoparticle is provided. The therapeutic nanoparticle comprises a hydrophobic ion-pair comprising a hydrophobic acid and a therapeutic agent having at least one ionizable amine moiety; wherein difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least about 1.0 pKa units, and about 50 to about 99.75 weight percent of a diblock poly(lactic) acid-poly(ethylene)glycol copolymer, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of about 15 kDa to about 20 kDa poly(lactic acid) and a number average molecular weight of about 4 kDa to about 6 kDa poly(ethylene)glycol.

[0013] In certain embodiments, the difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least about 2.0 pKa units. In other embodiments, the difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least about 4.0 pKa units.

[0014] In certain embodiments, the therapeutic nanoparticle comprises about 0.05 to about 20 weight percent of the hydrophobic acid.

[0015] In some embodiments, the substantially hydrophobic acid has a log P of about 2 to about 7.

[0016] In some embodiments, the substantially hydrophobic acid has a pK_a in water of about -1.0 to about 5.0. In other embodiments, the substantially hydrophobic acid has a pK_a in water of about 2.0 to about 5.0.

[0017] In certain embodiments, the substantially hydrophobic acid and the basic therapeutic agent form a hydrophobic ion pair in the therapeutic nanoparticle.

[0018] In some embodiments, the hydrophobic acid is a fatty acid. For example, in certain embodiments, the fatty acid is a saturated fatty acid selected from the group consisting of: caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, nonadecylic acid, arachidic acid, heneicosylic acid, behenic acid, tricosylic acid,

embodiments, the therapeutic nanoparticle comprises about 15 to about 25 weight percent poly(ethylene)glycol. In other embodiments, the therapeutic nanoparticle comprises about 20 to about 30 weight percent poly(ethylene)glycol.

[0028] In certain embodiments, the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of about 15kDa to about 20kDa poly(lactic acid) and a number average molecular weight of about 4kDa to about 6kDa poly(ethylene)glycol.

[0029] In some embodiments, the therapeutic nanoparticle further comprises about 0.2 to about 30 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand. In other embodiments, the therapeutic nanoparticle further comprises about 0.2 to about 30 weight percent poly(lactic) acid-co-poly(glycolic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand. In certain embodiments, the targeting ligand is covalently bound to the poly(ethylene)glycol.

[0030] In certain embodiments, the hydrophobic acid is a polyelectrolyte. For example, in some embodiments, the polyelectrolyte is selected from the group consisting of a poly(styrene sulfonic acid), polyacrylic acid, and polymethacrylic acid.

[0031] In certain embodiments, a contemplated therapeutic nanoparticle further comprises a mixture of two or more substantially hydrophobic acids. For example, in some embodiments, a contemplated therapeutic nanoparticle comprises a mixture of two substantially hydrophobic acids, a mixture of three substantially hydrophobic acids, a mixture of four substantially hydrophobic acids, or a mixture of five substantially hydrophobic acids.

[0032] ~~In another aspect, a~~A therapeutic nanoparticle is provided. The therapeutic nanoparticle is prepared by emulsification of a first organic phase comprising a first polymer, a basic therapeutic agent having a protonatable nitrogen, and a substantially hydrophobic 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.

[0033] ~~In yet another aspect, a~~A pharmaceutically acceptable composition is provided. The pharmaceutically acceptable composition comprises a plurality of contemplated therapeutic nanoparticles and a pharmaceutically acceptable excipient.

[0034] In certain embodiments, the pharmaceutically acceptable composition further comprises a saccharide. For example, in some embodiments, the saccharide is a disaccharide selected from the group consisting of sucrose or trehalose, or a mixture thereof.

[0035] In certain embodiments, the pharmaceutically acceptable composition further comprises a cyclodextrin. For example, in some embodiments, the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, heptakis-(2,3,6-tri-O-benzyl)-β-cyclodextrin, heptakis-(2,3,6-tri-O-benzoyl)-β-cyclodextrin, and mixtures thereof.

[0036] ~~In 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 contemplated therapeutic nanoparticle.

[0037] In some embodiments, the cancer is chronic myelogenous leukemia. In certain embodiments, 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, and mantle cell lymphoma.

[0038] ~~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 contemplated therapeutic nanoparticle.

[0039] ~~In yet another aspect, a~~A process for preparing a therapeutic nanoparticle is provided. The process comprises combining a first organic phase with a first aqueous solution to form a second phase, emulsifying the second phase to form an emulsion phase, wherein the emulsion phase comprises a first polymer, a basic therapeutic agent having a protonatable nitrogen, and a substantially hydrophobic acid, quenching of the emulsion phase thereby forming a quenched phase, and filtering the quenched phase to recover the therapeutic nanoparticles.

[0040] In some embodiments, the process further comprises combining the basic therapeutic agent and the substantially hydrophobic acid in the second phase prior to emulsifying the second phase. In certain embodiments, the basic therapeutic agent and the substantially hydrophobic acid form a hydrophobic ion pair prior to emulsifying the second phase. In certain other embodiments, the basic therapeutic agent and the substantially hydrophobic acid form a hydrophobic ion pair prior during emulsification of the second phase. In certain embodiments, the process further comprises combining the basic therapeutic agent and the substantially hydrophobic acid in the second phase substantially concurrently with emulsifying the second phase. For example, in some embodiments, the first organic phase

comprises the basic therapeutic agent and the first aqueous solution comprises the substantially hydrophobic acid.

[0041] In some embodiments, the basic therapeutic agent, when protonated, has a first pK_a, the substantially hydrophobic acid has a second pK_a, and the emulsion phase is quenched with an aqueous solution having a pH equal to a pK_a unit between the first pK_a and the second pK_a. For example, in certain embodiments, the quenched phase has a pH equal to a pK_a unit between the first pK_a and the second pK_a. In other embodiments, the basic therapeutic agent, when protonated, has a first pK_a, the substantially hydrophobic acid has a second pK_a, and the first aqueous solution has a pH equal to a pK_a unit between the first pK_a and the second pK_a. In certain other embodiments, the pH is equal to a pK_a unit that is about equidistant between the first pK_a and the second pK_a.

[0042] ~~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.

[0043] ~~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.

[0044] ~~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.

[0045] ~~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.

[0046] ~~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.

[0047] ~~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.

[0048] ~~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.

[0049] ~~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.

[0050] ~~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.

[0051] ~~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.

[0052] ~~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.

[0053] ~~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.

[0054] ~~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.

[0055] ~~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

[0056] Figure 1 is flow chart for an emulsion process for forming a disclosed nanoparticle.

[0057] Figures 2A and 2B show flow diagrams for a disclosed emulsion process.

[0058] Figure 3 depicts *in vitro* release profiles for sunitinib-containing nanoparticle formulations.

17. The therapeutic nanoparticle of claim 15, wherein the fatty acid is an omega-3 fatty acid selected from the group consisting of: hexadecatrienoic acid, alpha-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosatetraenoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, and combinations thereof.

18. The therapeutic nanoparticle of claim 15, wherein the fatty acid is an omega-6 fatty acid selected from the group consisting of: linoleic acid, gamma-linolenic acid, eicosadienoic acid, dihomo-gamma-linolenic acid, arachidonic acid, docosadienoic acid, adrenic acid, docosapentaenoic acid, tetracosatetraenoic acid, tetracosapentaenoic acid, and combinations thereof.

19. The therapeutic nanoparticle of claim 15, wherein the fatty acid is an omega-9 fatty acid selected from the group consisting of: oleic acid, eicosenoic acid, mead acid, erucic acid, nervonic acid, and combinations thereof.

20. The therapeutic nanoparticle of claim 15, wherein the fatty acid is a polyunsaturated fatty acid selected from the group consisting of: rumenic acid, α-calendic acid, β-calendic acid, jacaric acid, α-eleostearic acid, β-eleostearic acid, catalpic acid, punicic acid, rumelenic acid, α-parinaric acid, β-parinaric acid, bosseopentaenoic acid, pinolenic acid, podocarpic acid, and combinations thereof.

21. The therapeutic nanoparticle of any one of claims 1-14, wherein the hydrophobic acid is a bile acid.

22. The therapeutic nanoparticle of claim 21, wherein the bile acid is selected from the group consisting of chenodeoxycholic acid, ursodeoxycholic acid, deoxycholic acid, hycholic acid, beta-muricholic acid, cholic acid, lithocholic acid, an amino acid-conjugated bile acid, and combinations thereof.

23. The therapeutic nanoparticle of claim 22, wherein the amino acid-conjugated bile acid is a glycine-conjugated bile acid or a taurine-conjugated bile acid.

24. The therapeutic nanoparticle of ~~any one of~~ claim~~s~~ 14, wherein the hydrophobic acid is selected from the group consisting of dioctyl sulfosuccinic acid, 1-hydroxy-2-naphthoic acid, dodecylsulfuric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, pamoic acid, undecanoic acid, and combinations thereof.

25. The therapeutic nanoparticle of any one of claims 1-24, comprising about 1 to about 15 weight percent of the protonatable nitrogen-containing therapeutic agent.

63. Use of a composition comprising the therapeutic nanoparticle of any one of claims 1-57 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 1-57~~.

64. The ~~method~~ use of claim 63, wherein the cancer is chronic myelogenous leukemia.

65. The ~~method~~ use of claim 63, 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, and mantle cell lymphoma.

66. Use of a composition comprising the therapeutic nanoparticle of any one of claims 1-57 in the manufacture of a medicament for ~~A method of~~ treating a gastrointestinal stromal tumor 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 1-57~~.

67. A process for preparing a therapeutic nanoparticle, comprising:

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

emulsifying the second phase to form an emulsion phase, wherein the emulsion phase comprises a first polymer, a basic therapeutic agent having a protonatable nitrogen, and a substantially hydrophobic acid;

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

filtering the quenched phase to recover the therapeutic nanoparticles.

68. The process of claim 67, further comprising combining the basic therapeutic agent and the substantially hydrophobic acid in the second phase prior to emulsifying the second phase.

69. The process of claim 68, wherein the basic therapeutic agent and the substantially hydrophobic acid form a hydrophobic ion pair prior to emulsifying the second phase.

70. The process of claim 68, wherein the basic therapeutic agent and the substantially hydrophobic acid form a hydrophobic ion pair prior during emulsification of the second phase.

71. The process of claim 67, further comprising combining the basic therapeutic agent and the substantially hydrophobic acid in the second phase substantially concurrently with emulsifying the second phase.

72. The process of claim 71, wherein the first organic phase comprises the basic therapeutic agent and the first aqueous solution comprises the substantially hydrophobic acid.

73. The process of any one of claims 67-72, wherein the basic therapeutic agent, when protonated, has a first pK_a, the substantially hydrophobic acid has a second pK_a, and the emulsion phase is quenched with an aqueous solution having a pH equal to a pK_a unit between the first pK_a and the second pK_a.

74. The process of claim 73, wherein the quenched phase has a pH equal to a pK_a unit between the first pK_a and the second pK_a.

75. The process of any one of claims claim 67-74, wherein the basic therapeutic agent, when protonated, has a first pK_a, the substantially hydrophobic acid has a second pK_a, and the first aqueous solution has a pH equal to a pK_a unit between the first pK_a and the second pK_a.

76. The process of any one of claims 73-75, wherein the pH is equal to a pK_a unit that is about equidistant between the first pK_a and the second pK_a.

77. A composition comprising the therapeutic nanoparticle of any one of claims 1-57 for use in treating cancer in a patient in need thereof.

78. A composition comprising the therapeutic nanoparticle of any one of claims 1-57 for use in treating a gastrointestinal stromal tumor in a patient in need thereof.