[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:~~

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

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

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

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

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

0.2 to 20 weight percent of a basic therapeutic agent having a protonatable nitrogen; wherein the pKa of the basic therapeutic agent is at least 1.0 pK_a units greater than the pK_a of the hydrophobic acid, wherein the basic therapeutic agent is a kinase inhibitor selected from the group consisting of sunitinib, imatinib, nilotinib, dasatinib, bosutunib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof; and

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

[~~0006c~~0006b] In a ~~third~~ second 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 1.0 pKa units, wherein the basic therapeutic agent is a kinase inhibitor selected from the group consisting of sunitinib, imatinib, nilotinib, dasatinib, bosutunib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof; and

50 to 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 15 kDa to 20 kDa poly(lactic acid) and a number average molecular weight of 4 kDa to 6 kDa poly(ethylene)glycol.

[~~0006d~~0006c] In a ~~fourth~~ third aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles as disclosed herein, a pharmaceutically acceptable excipient and a cyclodextrin.

[~~0006e~~0006d] In a ~~fifth~~ fourth 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.

CLAIMS

~~1. A therapeutic nanoparticle comprising:~~

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

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

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

~~2~~1. A therapeutic nanoparticle comprising:

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

0.2 to 20 weight percent of a basic therapeutic agent having a protonatable nitrogen; wherein the pKa of the basic therapeutic agent is at least 1.0 pK_a units greater than the pK_a of the hydrophobic acid, wherein the basic therapeutic agent is a kinase inhibitor selected from the group consisting of sunitinib, imatinib, nilotinib, dasatinib, bosutunib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof; and

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

~~3~~2. The therapeutic nanoparticle of claim ~~2~~1, wherein the molar ratio of the hydrophobic acid to the basic therapeutic agent is 0.5:1 to 1.5:1.

43. The therapeutic nanoparticle of claim ~~2~~1, wherein the molar ratio of the hydrophobic acid to the basic therapeutic agent is 0.75:1 to 1.25:1.

~~5~~4. The therapeutic nanoparticle of any one of claims 1-43, wherein the pK_a of the basic therapeutic agent is at least 2.0 pK_a units greater than the pK_a of the hydrophobic acid.

~~6~~5. The therapeutic nanoparticle of any one of claims 1-43, wherein the pK_a of the basic therapeutic agent is at least 4.0 pK_a units greater than the pK_a of the hydrophobic acid.

~~7~~6. 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 1.0 pKa units, wherein the basic therapeutic agent is a kinase inhibitor selected from the group consisting of sunitinib, imatinib, nilotinib, dasatinib, bosutunib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof; and

50 to 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 15 kDa to 20 kDa poly(lactic acid) and a number average molecular weight of 4 kDa to 6 kDa poly(ethylene)glycol.

~~8~~7. The therapeutic nanoparticle of claim ~~7~~6, wherein the difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least 2.0 pKa units.

~~9~~8. The therapeutic nanoparticle of claim ~~7~~6, wherein the difference between the pKa of the basic therapeutic agent and the hydrophobic acid is at least 4.0 pKa units.

~~10~~9. The therapeutic nanoparticle of any one of claims ~~7-9~~6-8, comprising 0.05 to 20 weight percent of the hydrophobic acid.

~~11~~10. The therapeutic nanoparticle of any one of claims 1-~~10~~9, wherein the hydrophobic acid has a logP of 2 to 7.

~~12~~11. The therapeutic nanoparticle of any one of claims 1-~~11~~10, wherein the hydrophobic acid has a pK_a in water of -1.0 to 5.0.

~~13~~12. The therapeutic nanoparticle of any one of claims 1-~~11~~10, wherein the hydrophobic acid has a pK_a in water of 2.0 to 5.0.

~~14~~13. The therapeutic nanoparticle of any one of claims 1-~~13~~12, wherein the hydrophobic acid and the basic therapeutic agent form a hydrophobic ion pair in the therapeutic nanoparticle.

~~15~~14. The therapeutic nanoparticle of any one of claims 1-~~14~~13, wherein the hydrophobic acid is a fatty acid.

~~16~~15. The therapeutic nanoparticle of claim ~~15~~14, wherein 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, lignoceric acid, pentacosylic acid, cerotic acid, heptacosylic acid, montanic acid, nonacosylic acid, melissic acid, henatriacontylic acid, lacceroic acid, psyllic acid, geddic acid, ceroplastic acid, hexatriacontylic acid, and combinations thereof.

~~17~~16. The therapeutic nanoparticle of claim ~~15~~14, 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~~17. The therapeutic nanoparticle of claim ~~15~~14, 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~~18. The therapeutic nanoparticle of claim ~~15~~14, 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~~19. The therapeutic nanoparticle of claim ~~15~~14, 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~~20. The therapeutic nanoparticle of any one of claims 1-~~14~~13, wherein the hydrophobic acid is a bile acid.

~~22~~21. The therapeutic nanoparticle of claim ~~21~~20, 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~~22. The therapeutic nanoparticle of claim ~~22~~21, wherein the amino acid-conjugated bile acid is a glycine-conjugated bile acid or a taurine-conjugated bile acid.

~~24~~23. The therapeutic nanoparticle of claim ~~14~~13, 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~~24. The therapeutic nanoparticle of any one of claims 1-~~24~~23, comprising 1 to 15 weight percent of the protonatable nitrogen-containing therapeutic agent.

~~26~~25. The therapeutic nanoparticle of any one of claims 1-~~24~~23, comprising 2 to 15 weight percent of the protonatable nitrogen-containing therapeutic agent.

~~27~~26. The therapeutic nanoparticle of any one of claims 1-~~24~~23, comprising 4 to 15 weight percent of the protonatable nitrogen-containing therapeutic agent.

~~28~~27. The therapeutic nanoparticle of any one of claims 1-~~24~~23, comprising 5 to 10 weight percent of the protonatable nitrogen-containing therapeutic agent.

~~29~~28. The therapeutic nanoparticle of any one of claims 1-~~24~~23, wherein the hydrophobic acid has a molecular weight of between 300 Da and 1000 Da.

~~30. The therapeutic nanoparticle of any one of claims 1-29, wherein the therapeutic agent is a kinase inhibitor.~~

~~31. The therapeutic nanoparticle of claim 30, wherein the kinase inhibitor is a tyrosine kinase inhibitor selected from the group consisting of sunitinib, imatinib, nilotinib, dasatinib, bosutinib, ponatinib, bafetinib, and pharmaceutically acceptable salts thereof.~~

~~32~~29. The therapeutic nanoparticle of any one of claims 1-~~31~~28, wherein the hydrodynamic diameter of the therapeutic nanoparticle is 60 to 150 nm.

~~33~~30. The therapeutic nanoparticle of any one of claims 1-~~31~~28, wherein the hydrodynamic diameter is 90 to 140 nm.

~~34~~31. The therapeutic nanoparticle of any one of claims 1-~~33~~30, wherein the therapeutic nanoparticle retains the therapeutic agent for at least 1 minute when placed in a phosphate buffer solution at 37 °C.

~~35~~32. The therapeutic nanoparticle of any one of claims 1-~~34~~31, wherein the therapeutic nanoparticle immediately releases less than 30% of the therapeutic agent when placed in a phosphate buffer solution at 37 °C.

~~36~~33. The therapeutic nanoparticle of any one of claims 1-~~34~~31, wherein the therapeutic nanoparticle releases 10 to 45% of the therapeutic agent over 1 hour when placed in a phosphate buffer solution at 37 °C.

~~37~~34. The therapeutic nanoparticle of any one of claims 1-~~36~~33, wherein the therapeutic nanoparticle has a release profile that is the same as a release profile for a control nanoparticle that is the same as the therapeutic nanoparticle except that it does not contain a fatty acid or bile acid.

3835. The therapeutic nanoparticle of any one of claims 1-3734, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of 0.6 to 0.95.

3936. The therapeutic nanoparticle of any one of claims 1-3734, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of 0.6 to .8.

4037. The therapeutic nanoparticle of any one of claims 1-3734, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of 0.75 to 0.85.

4138. The therapeutic nanoparticle of any one of claims 1-3734, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of 0.7 to 0.9.

4239. The therapeutic nanoparticle of any one of claims 1-4138, wherein the therapeutic nanoparticle comprises 10 to 25 weight percent poly(ethylene)glycol.

4340. The therapeutic nanoparticle of any one of claims 1-4138, wherein the therapeutic nanoparticle comprises 10 to 20 weight percent poly(ethylene)glycol.

4441. The therapeutic nanoparticle of any one of claims 1-4138, wherein the therapeutic nanoparticle comprises 15 to 25 weight percent poly(ethylene)glycol.

4542. The therapeutic nanoparticle of any one of claims 1-4138, wherein the therapeutic nanoparticle comprises 20 to 30 weight percent poly(ethylene)glycol.

4643. The therapeutic nanoparticle of any one of claims 1-4542, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a number average molecular weight of 15kDa to 20kDa poly(lactic acid) and a number average molecular weight of 4kDa to 6kDa poly(ethylene)glycol.

4744. The therapeutic nanoparticle of any one of claims 1-4643, further comprising 0.2 to 30 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand.

4845. The therapeutic nanoparticle of any one of claims 1-4744, further comprising 0.2 to 30 weight percent poly(lactic) acid-co-poly(glycolic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand.

4946. The therapeutic nanoparticle of claim 47-44 or 4845, wherein the targeting ligand is covalently bound to the poly(ethylene)glycol.

~~50~~47. The therapeutic nanoparticle of any one of claims 1-~~49~~46, wherein the hydrophobic acid is a polyelectrolyte.

~~51~~48. The therapeutic nanoparticle of claim ~~50~~47, wherein the polyelectrolyte is selected from the group consisting of a poly(styrene sulfonic acid), polypolyacrylic acid, and polymethacrylic acid.

~~52~~49. The therapeutic nanoparticle of any one of claims 1-~~51~~48, further comprising a mixture of two or more hydrophobic acids.

~~53~~50. The therapeutic nanoparticle of claim ~~52~~49, comprising a mixture of two hydrophobic acids.

~~54~~51. The therapeutic nanoparticle of claim ~~52~~49, comprising a mixture of three hydrophobic acids.

~~55~~52. The therapeutic nanoparticle of claim ~~52~~49, comprising a mixture of four hydrophobic acids.

~~56~~53. The therapeutic nanoparticle of claim ~~52~~49, comprising a mixture of five hydrophobic acids.

~~57~~54. A pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles of any of claims 1-~~56~~53, a pharmaceutically acceptable excipient and a cyclodextrin.

~~58~~55. The pharmaceutically acceptable composition of claim ~~57~~54, further comprising a saccharide.

~~59~~56. The pharmaceutically acceptable composition of claim ~~58~~55, wherein the saccharide is a disaccharide selected from the group consisting of sucrose or trehalose, or a mixture thereof.

~~60~~57. The pharmaceutically acceptable composition of any of claims ~~57~~-54 to ~~59~~56, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, heptakis-(2,3,6-tri-O-benzyl)-β-cyclodextrin, and mixtures thereof.

~~61~~58. Use of a composition comprising the therapeutic nanoparticle of any one of claims 1-~~56~~53 in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof.