[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~~ 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 ~~about~~ 10 to ~~about~~ 30 weight percent ~~poly(ethylene)glycol~~ of the therapeutic nanoparticle.

[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~~ 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 ~~about~~ 10 to ~~about~~ 30 weight percent ~~poly(ethylene)glycol~~ of the therapeutic nanoparticle.

[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~~0006d] In a ~~fifth~~ fourth 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 and a cyclodextrin.

~~**[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~~0006e] In a ~~seventh~~ fifth 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] 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 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

CLAIMS

1. 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~~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 ~~about~~ 10 to ~~about~~ 30 weight percent ~~poly(ethylene)glycol~~of the therapeutic nanoparticle.

2. 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~~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 ~~about~~ 10 to ~~about~~ 30 weight percent ~~poly(ethylene)glycol~~of the therapeutic nanoparticle.

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

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

5. The therapeutic nanoparticle of any one of claims 1-4, wherein 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.

6. The therapeutic nanoparticle of any one of claims 1-4, wherein 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.

7. 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.

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

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

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

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

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

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

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

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

16. The therapeutic nanoparticle of claim 15, 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. 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 claim 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.

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

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

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

29. The therapeutic nanoparticle of any one of claims 1-24, wherein the hydrophobic acid has a molecular weight of between ~~about~~ 300 Da and ~~about~~ 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. The therapeutic nanoparticle of any one of claims 1-31, wherein the hydrodynamic diameter of the therapeutic nanoparticle is ~~about~~ 60 to ~~about~~ 150 nm.

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

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

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

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

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

38. The therapeutic nanoparticle of any one of claims 1-37, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of ~~about~~ 0.6 to ~~about~~ 0.95.

39. The therapeutic nanoparticle of any one of claims 1-37, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of ~~about~~ 0.6 to ~~about~~ 0.8.

40. The therapeutic nanoparticle of any one of claims 1-37, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of ~~about~~ 0.75 to ~~about~~ 0.85.

41. The therapeutic nanoparticle of any one of claims 1-37, wherein the poly(lactic) acid-poly(ethylene)glycol copolymer has a poly(lactic) acid number average molecular weight fraction of ~~about~~ 0.7 to ~~about~~ 0.9.

42. The therapeutic nanoparticle of any one of claims 1-41, wherein the therapeutic nanoparticle comprises ~~about~~ 10 to ~~about~~ 25 weight percent poly(ethylene)glycol.

43. The therapeutic nanoparticle of any one of claims 1-41, wherein the therapeutic nanoparticle comprises ~~about~~ 10 to ~~about~~ 20 weight percent poly(ethylene)glycol.

44. The therapeutic nanoparticle of any one of claims 1-41, wherein the therapeutic nanoparticle comprises ~~about~~ 15 to ~~about~~ 25 weight percent poly(ethylene)glycol.

45. The therapeutic nanoparticle of any one of claims 1-41, wherein the therapeutic nanoparticle comprises ~~about~~ 20 to ~~about~~ 30 weight percent poly(ethylene)glycol.

46. The therapeutic nanoparticle of any one of claims 1-45, wherein 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.

47. The therapeutic nanoparticle of any one of claims 1-46, further comprising ~~about~~ 0.2 to ~~about~~ 30 weight percent poly(lactic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand.

48. The therapeutic nanoparticle of any one of claims 1-47, further comprising ~~about~~ 0.2 to ~~about~~ 30 weight percent poly(lactic) acid-co-poly(glycolic) acid-poly(ethylene)glycol copolymer functionalized with a targeting ligand.

49. The therapeutic nanoparticle of claim 47 or 48, wherein the targeting ligand is covalently bound to the poly(ethylene)glycol.

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

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

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

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

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

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

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

~~57. 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.~~

~~58~~57. A pharmaceutically acceptable composition comprising a plurality of therapeutic nanoparticles of any of claims 1-~~57~~56, ~~and~~ a pharmaceutically acceptable excipient and a cyclodextrin.

~~59~~58. The pharmaceutically acceptable composition of claim ~~58~~57, further comprising a saccharide.

~~60. The pharmaceutically acceptable composition of claim 58 or 59, further comprising a cyclodextrin.~~

~~61~~59. The pharmaceutically acceptable composition of claim ~~59~~58, wherein the saccharide is a disaccharide selected from the group consisting of sucrose or trehalose, or a mixture thereof.

~~62~~60. The pharmaceutically acceptable composition of any of claims 57 to 59~~60~~, 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.

~~63. Use of a composition comprising the therapeutic nanoparticle of any one of claims 1-57 in the manufacture of a medicament for treating cancer in a patient in need thereof.~~

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

~~65. The 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.~~

~~6661~~. Use of a composition comprising the therapeutic nanoparticle of any one of claims 1-~~57~~ 56 in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof.

~~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.