[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:

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 is 10 to 30 weight percent of the therapeutic nanoparticle.

[0006b] In a 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 the pKa of the basic therapeutic agent is at least 1.0 pKa greater than 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, 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.

[0006c] In a 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.

[0006d] In a 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:

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 is 10 to 30 weight percent of the therapeutic nanoparticle.

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

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

4. The therapeutic nanoparticle of any one of claims 1-3, 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.

5. The therapeutic nanoparticle of any one of claims 1-3, 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.

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 the pKa of the basic therapeutic agent is at least 1.0 pKa greater than 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, 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.

7. The therapeutic nanoparticle of claim 6, wherein the pKa of the basic therapeutic agent is at least 2.0 pKa greater than the hydrophobic acid.

8. The therapeutic nanoparticle of claim 6, wherein the pKa of the basic therapeutic agent is at least 4.0 pKa greater than the hydrophobic acid.

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

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

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

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

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

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

15. The therapeutic nanoparticle of claim 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.