

CLAIMS

WHAT IS CLAIMED IS:

1. A sustained release composition comprising a therapeutic agent and a sustained release agent, wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and wherein the therapeutic agent has at least two percentage dissolution parameters selected from:
 - a percentage dissolution of less than 20% at 2 hours;
 - a percentage dissolution of less than 40% at 7 hours; and
 - a percentage dissolution of at least 30% at 12 hours,as measured at 37°C in simulated gastric fluid at pH 1.2 from hours 0 to 2 and in simulated intestinal fluid at pH 6.8 after 2 hours.
2. The sustained release composition of claim 1, wherein the therapeutic agent has at least three of the percentage dissolution parameters.
3. The sustained release composition of claim 1 or claim 2, wherein the therapeutic agent has percentage dissolution of less than 35% at 3 hours.
4. The sustained release composition of any one of claims 1-3, wherein the therapeutic agent has percentage dissolution ranging from 35% to 55% at 12 hours.
5. The sustained release composition of any one of claims 1-4, wherein the therapeutic agent has percentage dissolution of at least 50% at 24 hours.
6. The sustained release composition of any one of claims 1-5, wherein the therapeutic agent has percentage dissolution ranging from 65% to 85% at 24 hours.
7. The sustained release composition of any one of claims 1-6, wherein the sustained release agent is selected from the group consisting of a cellulosic ether, a gum, an acrylic resin, or a combination thereof.
8. The sustained release composition of any one of claims 1-7, wherein the sustained release agent is a hydroxyalkyl cellulose, a hydroxyethyl cellulose, a hydroxypropyl cellulose, a hydroxypropylmethyl cellulose, or a combination thereof.

9. The sustained release composition of any one of claims 1-8, wherein the sustained release agent is hypromellose.
10. A sustained release composition comprising:
a therapeutic agent, and
a sustained release agent,
wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and wherein the sustained release agent is selected from the group consisting of hydroxyalkyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.
11. The sustained release composition of any one of claims 1-10, comprising at least 1% w/w, at least 10% w/w, at least 20% w/w, at least 25% w/w, at least 30% w/w, at least 35% w/w, or at least 40% w/w of the sustained release agent.
12. The sustained release composition of any one of claims 1-11, comprising from 1% to 99% w/w of the sustained release agent.
13. The sustained release composition of any one of claims 1-12, comprising from 5% to 90% w/w of the sustained release agent.
14. The sustained release composition of any one of claims 1-12, comprising from 5% to 70% w/w of the sustained release agent.
15. The sustained release composition of any one of claims 1-12, comprising from 10% to 40% w/w of the sustained release agent.
16. The sustained release composition of any one of claims 1-12, comprising from 15% to 40% w/w of the sustained release agent.
17. The sustained release composition of any one of claims 1-16, comprising from 0.25% to 10% w/w, from 0.5% to 8% w/w, or from 1% to 4% w/w of the therapeutic agent.

18. The sustained release composition of any one of claims 1-17, wherein at least 90% w/w, at least 95% w/w, or at least 99% w/w of the therapeutic agent is Form I of (Z)-endoxifen, Form II of (Z)-endoxifen, Form III of (Z)-endoxifen, or a combination thereof.
19. The sustained release composition of any one of claims 1-18, further comprising a binder, a lubricant, or a combination thereof.
20. The sustained release composition of claim 19, wherein the binder is a monosaccharide, a disaccharide, a starch, a polyhedric alcohol, mannitol, xylitol, sorbitol, lactose, a polyethylene glycol, a gum, alginic acid, polyvinyl pyrrolidone, methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, crystalline cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, calcium carbonate, calcium phosphate, sodium carbonate, sodium phosphate, anhydrous dibasic calcium phosphate, talc, a dextrate, kaolin, mannitol, silicic acid, sorbitol, or a combination thereof.
21. The sustained release composition of claim 19 or claim 20, wherein the binder is microcrystalline cellulose.
22. The sustained release composition of any one of claims 19-21, comprising from 1% to 99% w/w of the binder.
23. The sustained release composition of any one of claims 19-21, comprising from 1% to 99% w/w of the binder.
24. The sustained release composition of any one of claims 19-21, comprising from 30% to 97% w/w of the binder.
25. The sustained release composition of any one of claims 19-21, comprising from 40% to 75% w/w of the binder.
26. The sustained release composition of any one of claims 19-21, comprising from 50% to 75% w/w of the binder.
27. The sustained release composition of any one of claims 19-26, wherein the lubricant is stearic acid, calcium stearate, magnesium stearate, zinc stearate, potassium stearate,

hydrogenated vegetable oil, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, a glycol, polyethylene glycol, sodium lauryl sulfate, magnesium lauryl sulfate, macrogol, talc, ethyl oleate, ethyl laureate, agar, waxes, or a combination thereof.

28. The sustained release composition of claim 27, wherein the lubricant is magnesium stearate.

29. The sustained release composition of any one of claims 1-28, further comprising an enteric coating enclosing a tablet comprising the therapeutic agent and the sustained release agent, wherein the enteric coating comprises:

- a delayed release agent;
- a plasticizer;
- an anti-tacking agent; or
- a combination thereof.

30. The sustained release composition of claim 29, wherein the enteric coating is from 4% to 40% w/w of the sustained release composition.

31. The sustained release composition of claim 29 or claim 30, wherein the enteric coating is from 5% to 30% w/w of the sustained release composition.

32. The sustained release composition of any one of claims 29-31, wherein the enteric coating is from 5% to 25% w/w of the sustained release composition.

33. The sustained release composition of any one of claims 29-31, wherein the enteric coating is from 5% to 20% w/w of the sustained release composition.

34. The sustained release composition of any one of claims 29-31, wherein the enteric coating is from 5% to 15% w/w of the sustained release composition.

35. The sustained release composition of any one of claims 29-34, wherein the delayed release agent is present at from 0.1% to 30% w/w of the enteric coating.

36. The sustained release composition of any one of claims 29-34, wherein the delayed release agent is present at from 5% to 25% w/w of the enteric coating.

37. The sustained release composition of any one of claims 29-34, wherein the delayed release agent is present at from 8% to 14% w/w of the enteric coating.
38. The sustained release composition of any one of claims 29-37, wherein the delayed release agent is a polymethacrylate.
39. The sustained release composition of any one of claims 1-38, further comprising a pharmaceutically acceptable excipient.
40. A sustained release composition comprising a tablet and an enteric coating enclosing the tablet, wherein the tablet comprises:
a therapeutic agent; and
a sustained release agent,
and wherein the enteric coating comprises:
a delayed release agent;
a plasticizer;
an anti-tacking agent; or
a combination thereof,
wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, wherein the sustained release agent is selected from the group consisting of hydroxyalkyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.
41. A sustained release composition comprising a tablet and an enteric coating enclosing the tablet, wherein the tablet comprises a therapeutic agent and hypromellose, wherein the therapeutic agent comprises at least 90% (Z)-endoxifen, and wherein the enteric coating comprises a poly(meth)acrylate polymer and triethyl citrate.
42. The sustained release composition of claim 41, wherein the enteric coating further comprises talc.
43. The sustained release composition of claim 41 or claim 42, wherein the tablet comprises at least 20% w/w hypromellose relative to the total tablet weight.

44. The sustained release composition of any one of claims 41-43, wherein the tablet comprises from 1% to 40% w/w therapeutic agent relative to the total tablet weight.
45. The sustained release composition of any one of claims 41-44, wherein the enteric coating comprises from 60% to 80% w/w poly(meth)acrylate polymer relative to the total enteric coating weight.
46. The sustained release composition of any one of claims 41-45, wherein the enteric coating comprises no more than 10% w/w triethyl citrate relative to the total enteric coating weight.
47. The sustained release composition of any one of claims 41-46, wherein the enteric coating comprises from 10% to 40% w/w talc relative to the total enteric coating weight.
48. A method of preparing a sustained release composition comprising:
combining and mixing:
 a therapeutic agent selected from a (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, and a combination thereof;
 a sustained release agent;
 a binder; and
 a lubricant; and
dry compressing the therapeutic agent, the at least one sustained release agent, the at least one binder, and the at least one lubricant to form a core tablet.
49. The method of claim 48, further comprising:
combining and mixing:
 at least one delayed release agent;
 at least one plasticizer; and
 at least one anti-tacking component or anti-adherent component, thereby forming a coating solution; and
substantially coating the core tablet with the coating solution, thereby forming a functional coating.
50. A method of administering a sustained release composition comprising to a subject in need thereof, the method comprising orally administering the sustained release composition to the subject in need thereof,

wherein the sustained release composition comprises a therapeutic agent and a sustained release agent, wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and

wherein the sustained release composition is formulated such less than 20% of the therapeutic agent dissolves 2 hours after administration and at least 30% of the therapeutic agent dissolves within 12 hours after administration.

51. The method of claim 50, wherein the sustained release composition is formulated such less than 40% of the therapeutic agent dissolves 7 hours after administration.

52. A method of administering a sustained release composition comprising to a subject in need thereof, the method comprising orally administering the sustained release composition to the subject in need thereof,

wherein the sustained release composition comprises a therapeutic agent and a sustained release agent, wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and

wherein the sustained release composition is formulated such less than 20% of the therapeutic agent dissolves in simulated gastric fluid after 2 hours and at least 30% of the therapeutic agent dissolves after 2 hours in simulated gastric fluid followed by 10 hours in simulated intestinal fluid.

53. The method of claim 52, wherein the sustained release composition is formulated such less than 40% of the therapeutic agent dissolves after 2 hours in simulated gastric fluid followed by 5 hours in simulated intestinal.

54. A method of administering a sustained release composition comprising to a subject in need thereof, the method comprising orally administering the sustained release composition to the subject in need thereof,

wherein the sustained release composition comprises a therapeutic agent and a sustained release agent, wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and

wherein the therapeutic agent exhibits a time to maximum observed concentration of at least 8 hours, at least 9 hours, at least 10 hours, at least 15 hours, at least 20 hours, or at least 24 hours in a serum of the subject.

55. A method of treating a subject in need thereof, wherein the subject has a disorder or is at risk of having the disorder, the method comprising administering to the subject the sustained release composition of any one of claims 1-47.

56. A method of treating a subject in need thereof, wherein the subject has a disorder or is at risk of having the disorder, the method comprising administering to the subject a sustained release composition comprising:

a therapeutic agent, and

a sustained release agent,

wherein the therapeutic agent is (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof, and wherein the sustained release agent is selected from the group consisting of hydroxyalkyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose.

57. The method of claim 55 or claim 56, wherein the disorder is a breast disorder.

58. The method of claim 57, wherein the breast disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, ductal carcinoma *in situ*, lobular carcinoma *in situ*, breast cancer, precocious puberty, or McCune-Albright Syndrome.

59. The method of any one of claims 55-58, wherein the sustained release composition is administered orally.

60. The method of any one of claims 55-59, wherein the therapeutic agent exhibits a time to maximum observed concentration of at least 8 hours, at least 9 hours, at least 10 hours, at least 15 hours, at least 20 hours, or at least 24 hours in a serum of the subject.

61. The method of any one of claims 55-60, wherein the sustained release composition is administered in combination with an additional therapeutic agent.

62. The method of claim 61, wherein the additional therapeutic agent is a selective serotonin-reuptake inhibitor.

63. The method of claim 62, wherein the selective serotonin-reuptake inhibitor is selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.
64. The method of any one of claims 55-63, wherein the subject has a statistically significant alteration of a level of a biomarker in a tissue or fluid of the subject relative to a level of the biomarker in a normal subject.
65. The method of claim 64, wherein the biomarker is selected from the group consisting of: Ki-67, estrogen receptor, progesterone receptor, proliferating cell nuclear antigen, phosphor-histone H3, p16, p12, beta-galactosidase, terminal deoxynucleotidyl transferase dUTP nick end labeling, and an RNA sequence, or a combination thereof.
66. The method of claim 64 or claim 65, wherein the level of the biomarker in the tissue of the subject is reduced following administration of the sustained release composition.
67. The method of claim 64 or claim 65, wherein the level of the biomarker in the tissue of the subject is increased following administration of the sustained release composition.
68. The method of any one of claims 64-67, wherein the tissue is a diseased tissue.
69. The method of any one of claims 55-68, wherein the sustained release composition is administered to the subject for from 14 days to 40 days, from 10 days to 50 days, from 10 days to 40 days, from 10 days to 35 days, from 10 days to 30 days, from 10 days to 25 days, from 12 days to 50 days, from 12 days to 40 days, from 12 days to 35 days, from 12 days to 30 days, from 12 days to 25 days, from 12 days to 45 days, from 12 days to 30 days, from 14 days to 30 days, from 14 days to 50 days, from 14 days to 40 days, from 14 days to 35 days, from 14 days to 30 days, from 14 days to 25 days, from 16 days to 50 days, from 16 days to 40 days, from 16 days to 35 days, from 16 days to 30 days, from 16 days to 25 days, from 18 days to 50 days, from 18 days to 40 days, from 18 days to 35 days, from 18 days to 30 days, from 18 days to 25 days.
70. The method of any one of claims 55-69, wherein the sustained release composition is administered once per day, twice per day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, or every 7 days.

71. The method of any one of claims 55-70, wherein from 1 mg to 4 mg, from 2 mg to 4 mg, from 2 mg to 6 mg, from 2 mg to 8 mg, from 1 mg to 10 mg, from 1 mg to 12 mg, from 1 mg to 16 mg, from 2 mg to 10 mg, from 2 mg to 12 mg, from 2 mg to 16 mg, from 3 mg to 10 mg, from 3 mg to 12 mg, from 3 mg to 16 mg, from 4 mg to 10 mg, from 4 mg to 12 mg, or from 4 mg to 16 mg of the sustained release composition is administered to the subject per dose.