CLAIMS

WHAT IS CLAIMED IS:

1. A sustained release composition comprising a core tablet coated with an enteric coating, wherein the core tablet comprises:

a therapeutic agent comprising (Z)-endoxifen,

a sustained release agent, and

a hardness of not less than 4 kilopond (Kp) and not more than 16 Kp; and

wherein the enteric coating comprises a delayed release agent.

2. The sustained release composition of claim 1, wherein the therapeutic agent comprises at least 90% (Z)-endoxifen by weight relative to total therapeutic agent weight.

3. The sustained release composition of claim 1 or claim 2, wherein the core tablet comprises not less than 1% and not more than 40% therapeutic agent by weight relative to total core tablet weight.

4. The sustained release composition of any one of claims 1-3, wherein the sustained release agent comprises an hydroxyalkyl cellulose, a cellulosic ether, a gum, an acrylic resin, or a combination thereof.

5. The sustained release composition of claim 4, wherein the hydroxyalkyl cellulose comprises hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, or hydroxypropyl methylcellulose.

6. The sustained release composition of any one of claims 1-5, wherein the core table comprises not less than 5% and not more than 70%, or not less than 10% and not more than 40% of sustained release agent by weight relative to total core tablet weight.

7. The sustained release composition of any one of claims 1-6, wherein the core tablet comprises not less than 5% and not more than 60% hydroxypropyl methylcellulose by weight relative to total core tablet weight.

8. The sustained release composition of any one of claims 1-7, wherein the core tablet further comprises a binding agent.

9. The sustained release composition of claim 8, wherein the core tablet comprises not less than 30% and not more than 97%, or not less than 40% and not more than 75% of the binding agent by weight relative to total core tablet weight.

10. The sustained release composition of claim 8 or claim 9, wherein the binding agent comprises a monosaccharide, a disaccharide, a starch, a polyhydric alcohol, mannitol, xylitol, sorbitol, lactose, a polyethylene glycol, a gum, alginic acid, polyvinyl pyrrolidone, methyl cellulose, 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, silicic acid, or a combination thereof.

11. The sustained release composition of claim 10, wherein the core tablet comprises not less than 10% and not more than 90% microcrystalline cellulose by weight relative to total core tablet weight.

12. The sustained release composition of any one of claims 1-11, wherein the core tablet further comprises a lubricant.

13. The sustained release composition of claim 12, wherein the lubricant comprises 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, talc, ethyl oleate, ethyl laureate, agar, waxes, or a combination thereof.

14. The sustained release composition of claim 13, wherein the core tablet comprises not less than 0.01% and not more than 5% magnesium stearate by weight relative to total core tablet weight.

15. The sustained release composition of any one of claims 1-14, wherein the delayed release agent comprises a poly(meth)acrylate polymer.

16. The sustained release composition of claim 15, wherein the enteric coating comprises not less than 60% and not more than 80% of the poly(meth)acrylate polymer by weight relative to total enteric coating weight.

17. The sustained release composition of any one of claims 1-16, wherein the enteric coating further comprises a plasticizer.

18. The sustained release composition of claim 17, wherein the plasticizer comprises triethyl citrate.

19. The sustained release composition of claim 18, wherein the enteric coating comprises not less than 0.01% and not more than 5% triethyl citrate by weight relative to total enteric coating weight.

20. The sustained release composition of any one of claims 1-19, wherein the enteric coating further comprises an anti-adherent agent.

21. The sustained release composition of claim 20, wherein the anti-adherent agent comprises talc.

22. The sustained release composition of claim 21, wherein the enteric coating comprises not less than 1% and not more than 40% talc by weight relative to total enteric coating weight.

23. The sustained release composition of any one of claims 1-22, wherein the enteric coating constitutes not less than 5% and not more than 30%, not less than 5% and not more than 25%, or not less than 5% and not more than 20% by weight of total sustained release composition weight.

24. The sustained release composition of any one of claims 1-23, wherein the (Z)-endoxifen comprises a (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof.

25. The sustained release composition of any one of claims 1-24, wherein the therapeutic agent has a percentage dissolution of less than 20% at 2 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.

26. The sustained release composition of any one of claims 1-25, wherein the therapeutic agent has a percentage dissolution of less than 40% at 7 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.

27. The sustained release composition of any one of claims 1-26, wherein the therapeutic agent has 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.

~~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~~28. The sustained release composition of ~~claim 1 or claim 2~~any one of claims 1-27, wherein the therapeutic agent has a 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~~29. The sustained release composition of any one of claims 1-~~4~~28, wherein the therapeutic agent has a 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~~30. The sustained release composition of any one of claims 1-~~17~~29, wherein at least 90% ~~w/w~~, at least 95% ~~w/w~~, or at least 99% ~~w/w~~by weight of the therapeutic agent is polymorphic Form I of (Z)-endoxifen, polymorphic Form II of (Z)-endoxifen, polymorphic Form III of (Z)-endoxifen, or a combination thereof.

31. The sustained release composition of any one of claims 1-30, wherein at least 90%, at least 95%, or at least 99% by weight of the therapeutic agent is polymorphic Form III of (Z)-endoxifen.

32. The sustained release composition of claim 30 or claim 31, wherein polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, or combinations 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~~33. Use of a sustained release composition in the manufacture of a medicament for treating a breast disorder, wherein the sustained release composition is formulated for oral administration~~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~~34. The ~~method~~ use of claim ~~50~~33, 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~~35. Use of the sustained release composition of any one of claims 1-32 in the manufacture of a medicament for treating a breast disorder in a subject in need thereof~~A method of treating a subject in need thereof~~, wherein the subject has ~~a~~ the breast disorder or is at risk of having the breast 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~~36. The use~~method~~ of ~~claim 57~~any one of claims 33-35, 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~~37. The use~~method~~ of ~~any one of claims 55-58~~claim 35, wherein the sustained release composition is to be administered orally.

~~60~~38. The ~~method~~ use of any one of claims ~~55~~35-~~59~~37, 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.

39. The sustained release composition of any one of claims 1-32 for use in a therapy.

~~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.~~