publications WO2019051416 (A1) and WO2019051370 (A1) describe methods of making (Z)-endoxifen and compositions using (Z)-endoxifen. WO2019051416 (A1) describes an enteric (delayed release) API-in-capsule comprising (Z)-endoxifen free base, crystalline forms/polymorphs and salts thereof, and WO2019051370 (A1) describes topical compositions comprising (Z)-endoxifen free base and salts thereof. None of these describe the matrix tablet-type sustained release preparations relating to (Z)-endoxifen, or polymorphs or salts thereof wherein the active drug (Z)-endoxifen is released over a prolonged period of time, for example over 4 to 24 hours or from at least 2 hours to at least 72 hours.

[0007a] In one aspect, the present disclosure refers to 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 from 10 kilopond (Kp) to 16 Kp; and

wherein the enteric coating comprises a delayed release agent.

[0007b] In another aspect, the present disclosure refers to a 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,

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, wherein the therapeutic agent comprises at least 90% (Z)-endoxifen free base, a polymorph of (Z)-endoxifen, a salt of (Z)-endoxifen, or a combination thereof by weight relative to total therapeutic agent weight, and

wherein the sustained release composition is formulated as a tablet with a hardness from 10 kilopond (Kp) to 16 Kp.

[0007c] In another aspect, the present disclosure refers to a use of the sustained release composition as described herein in the manufacture of a medicament for treating a breast disorder in a subject in need thereof, wherein the subject has the breast disorder or is at risk of having the breast disorder.

[0007d] In another aspect, the present disclosure refers to the sustained release composition as described herein for use in a therapy.

[0008] The present disclosure provides novel sustained release compositions comprising Z-endoxifen, and polymorphs and salts thereof, and methods of making them. Non-limiting exemplary sustained release compositions in the form of sustained release tablets as well as enteric coated delayed release tablets and capsules are provided in the present disclosure. Sustained release compositions of the present disclosure provide certain advantages: novel

sustained release (Z)-endoxifen compositions can be prepared by the methods disclosed herein and such sustained release compositions are stable, even at low doses. Since the sustained release compositions release (Z)-endoxifen or a polymorph or a salt thereof in slow and sustained manner, the maximum drug concentration (C_{max}) can be controlled in subject; high blood concentration and/or accumulation in a subject can be avoided or controlled, reducing the possibility of systemic and/or local side effects and toxicity. Subjects can be administered sustained release compositions of the present disclosure in lower doses or as necessary to reduce the side effects and ensure patient compliance. Further, the enteric coating of the sustained release compositions of the present disclosure provides surprisingly greater protection to (Z)-endoxifen in preventing or reducing the interconversion of active (Z)-endoxifen form to its inactive form, (E)-endoxifen, in the stomach resulting in greater amounts of (Z)-endoxifen release in the intestines. The unexpected advantages of suppressing this interconversion results in greater overall delivery of (Z)-endoxifen, and also aids in providing a slower, consistent release of the therapeutic agent. Targeting the small intestines, for example, the duodenum and colon, using enteric coated delayed release compositions increases the bioavailability of the drug in a subject, potentially increasing efficacy of the drug, and increases the potential of the compositions to withstanding the “food effect” (*e.g.*, decreases susceptibility to physical stimulation by eating). The enteric coated delayed release tablets and capsules of the present disclosure are protected from the acidic environment of the stomach and release Z-endoxifen, and polymorphs and salts thereof in the small and large intestines, for example at least 2 hours post ingestion of the dose.

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 tablet 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.

28. The sustained release composition of any one of claims 1-27, wherein the therapeutic agent has a percentage dissolution of less than 35% at 3 hours.

29. The sustained release composition of any one of claims 1-28, wherein the therapeutic agent has a percentage dissolution of at least 50% at 24 hours.

30. The sustained release composition of any one of claims 1-29, wherein at least 90%, at least 95%, or at least 99% 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, or combinations thereof.

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,

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.

34. The use of claim 33, wherein the sustained release composition is formulated such less than 40% of the therapeutic agent dissolves 7 hours after administration.

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, wherein the subject has the breast disorder or is at risk of having the breast disorder.

36. The use of 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.

37. The use of claim 35, wherein the sustained release composition is to be administered orally.

38. The use of any one of claims 35-37, 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.