7,485,623; 7,507,769; 7,704,516; 7,786,172; 7,968,532; and 8,048,927), endoxifen (*see*, US9,333,190; U.S. Patent Nos. 9,220,680; 9,090,640; and 9,200,045; U.S. Publication Nos. 2009/0291134, US20100112041, 20180049999, WO2019051416 (A1) and WO2019051370 (A1) Atossa Genetics), and their derivatives (*see*, U.S. Patent Nos. 8,063,249; U.S. Publication Nos. 2015/0080339 and 2014/0193334,). It is widely accepted that (Z)-endoxifen is the main active metabolite of tamoxifen responsible for the clinical efficacy of tamoxifen. Endoxifen is primarily generated via CYP2D6 mediated hydroxylation and CYP3A4-mediated N-demethylation of tamoxifen. Any drug that can be a substrate of CYP3A4 or CYP2D6, especially CYP2D6 (*e.g.*, SSRIs), can decrease the level of endoxifen and thus reduce the therapeutic benefits of tamoxifen. Administering endoxifen directly to such subjects circumnavigates the effects of such drug interactions.

[0005] While hydrochloride and citrate salts of endoxifen (*See, e.g.*, Fauq *et al.*, Bioorganic & Medicinal Chemistry Letters. 20 (2010) 3036 – 3038; Stearns *et al.*, J. Natl. Cancer Inst. Vol 95, No. 23, 2003; US Publication Nos. 2009/0291134 and 2010/0112041; Clinical Trials Gov. Identifier Nos. NCT01273168 and NCT02311933; Goetz et al., 2015, San Antonio Cancer Symposium; Ahmad *et al.*, Clinical Pharmacology & Therapeutics. 88(6) 814-817, 2010; and J Clin. Oncol. 30, 2012 (suppl; abstr 3089); Ahmad et al. Breast Cancer Research and Treatment 2010, 122, 579-584) are known in the art and currently under evaluation for metastatic cancer, there remains unmet medical need for new compositions and methods for the treatment and/or prevention of hormone dependent breast and reproductive tract (gynecologic) disorders and other disorders that are susceptible or responsive to endoxifen.

[0006] A strong need exists for methods to treat and to prevent breast diseases without significant adverse systemic side effects in men and women, particularly in the tamoxifen-refractory patients and in premenopausal population of women. A strong need also exists for formulations that provide blood levels of endoxifen that avoid rapid release or delivery of endoxifen in a subject that may be associated with side effects or tolerance issues for the patients. Further, a strong need also exists to ensure that a full amount of the (Z)-endoxifen dose is available to the patient, by ensuring the drug passes through the stomach without degradation in its acidic environment. In particular, there is a need for breast cancer treatments and preventatives that have reduced interactive effect with other medications or their metabolism.

SUMMARY

[0007] Endoxifen free base and endoxifen salts of prior publications and patent and patent applications have been developed for treatment of subjects with breast cancers. US 9,333,190 describes enteric-coated tablets and enteric-coated capsules made with endoxifen citrate. Patent

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 not less than 4 kilopond (Kp) and not more than 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.

[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.

[0009] In various examples, the present disclosure provides 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.

[0010] In some examples, the therapeutic agent has at least three of the percentage dissolution parameters. In some examples, the therapeutic agent has percentage dissolution of less than 35% at 3 hours. In some examples, the therapeutic agent has percentage dissolution ranging from 35% to 55% at 12 hours. In some examples, the therapeutic agent has percentage dissolution of at least 50% at 24 hours. In some examples, the therapeutic agent has percentage dissolution ranging from 65% to 85% at 24 hours. In some examples, the sustained release agent is selected from the group consisting of a cellulosic ether, a gum, an acrylic resin, or a combination thereof.

[0011] In some examples, the sustained release agent is a hydroxyalkyl cellulose, a hydroxyethyl cellulose, a hydroxypropyl cellulose, a hydroxypropylmethyl cellulose, or a combination thereof. In some examples, the sustained release agent is hypromellose.

[0012] In various examples, the present disclosure provides 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.

[0013] In some examples, the sustained release composition comprises 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. In some examples, the sustained release composition comprises from 1% to 99% w/w of the sustained release agent. In some examples, the sustained release composition comprises from 5% to 90% w/w of the sustained release agent. In some examples, the sustained release composition comprises from 5% to 70% w/w of the sustained release agent. In some examples, the sustained release composition comprises from 10% to 40% w/w of the sustained release agent. In some examples, the sustained release composition comprises from 15% to 40% w/w of the sustained release agent. In some examples, the sustained release agent comprises 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.

[0014] In some examples, 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.

[0015] In some examples, the sustained release composition further comprises a binder, a lubricant, or a combination thereof. In some examples, 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. In some examples, the binder is microcrystalline cellulose. In some examples, the sustained release composition comprises from 1% to 99% w/w of the binder. In some examples, the sustained release composition comprises from 1% to 99% w/w of the binder. In some examples, the sustained release composition comprises from 30% to 97% w/w of the binder. In some examples, the sustained release composition comprises from 40% to 75% w/w of the binder. In some examples, the sustained release composition comprises from 50% to 75% w/w of the binder.

[0016] In some examples, 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. In some examples, the lubricant is magnesium stearate.

[0017] In some examples, the sustained release composition further comprises 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. In some examples, the enteric coating is from 4% to 40% w/w of the sustained release composition. In some examples, the enteric coating is from 5% to 30% w/w of the sustained release composition. In some examples, the enteric coating is from 5% to 25% w/w of the sustained release composition. In some examples, the enteric coating is from 5% to 20% w/w of the sustained release composition. In some examples, the enteric coating is from 5% to 15% w/w of the sustained release composition.

[0018] In some examples, the delayed release agent is present at from 0.1% to 30% w/w of the enteric coating. In some examples, the delayed release agent is present at from 5% to 25% w/w of the enteric coating. In some examples, the delayed release agent is present at from 8% to 14% w/w of the enteric coating. In some examples, the delayed release agent is a polymethacrylate.

[0019] In some examples, the sustained release composition further comprises a pharmaceutically acceptable excipient.

[0020] In various examples, the present disclosure provides 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.

[0021] In various examples, the present disclosure provides 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.

[0022] In some examples, the enteric coating further comprises talc. In some examples, the tablet comprises at least 20% w/w hypromellose relative to the total tablet weight. In some examples, the tablet comprises from 1% to 40% w/w therapeutic agent relative to the total tablet weight. In some examples, the enteric coating comprises from 60% to 80% w/w poly(meth)acrylate polymer relative to the total enteric coating weight. In some examples, the enteric coating comprises no more than 10% w/w triethyl citrate relative to the total enteric coating weight. In some examples, the enteric coating comprises from 10% to 40% w/w talc relative to the total enteric coating weight.

[0023] In various examples, the present disclosure provides 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.

[0024] In some examples, the method further comprises 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.

[0025] In various examples, the present disclosure provides 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.

[0026] In some examples, the sustained release composition is formulated such less than 40% of the therapeutic agent dissolves 7 hours after administration.

[0027] In various examples, the present disclosure provides 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.

[0028] In some examples, 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.

[0029] In various examples, the present disclosure provides 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.

[0030] In various examples, the present disclosure provides 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 the present disclosure.

[0031] In various examples, the present disclosure provides 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.

[0032] In some examples, the disorder is a breast disorder. In some examples, 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. In some examples, the sustained release composition is administered orally. In some examples, 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.

[0033] In some examples, the sustained release composition is administered in combination with an additional therapeutic agent. In some examples, the additional therapeutic agent is a selective serotonin-reuptake inhibitor. In some examples, the selective serotonin-reuptake inhibitor is selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

[0034] In some examples, 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. In some examples, 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. In some examples, the level of the biomarker in the tissue of the subject is reduced following administration of the sustained release composition. In some examples, the level of the biomarker in the tissue of the subject is increased following administration of the sustained release composition. In some examples, the tissue is a diseased tissue.

[0035] In some examples, 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. In some examples, 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. In some examples, 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.

INCORPORATION BY REFERENCE

[0036] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0038] Figure 1 shows percentage dissolution and release of (Z)-endoxifen from sustained release compositions in the form of a sustained release tablet (uncoated) containing 4 mg of (Z)-endoxifen free base in comparison to control (a 4 mg delayed release neat (Z)-endoxifen free base active pharmaceutical ingredient (API)-in-capsule), as measured according to United States Pharmacopeia (USP) I method. (Z)-endoxifen release upon dissolution of the compositions was measured using high performance liquid chromatography with ultraviolet detection (HPLC-UV).

[0039] Figure 2 shows percentage dissolution and release of (Z)-endoxifen from exemplary sustained release compositions in the form of a sustained release tablet (uncoated) and an enteric coated delayed release tablet containing 4 mg of (Z)-endoxifen free base, as measured according to USP I method. (Z)-endoxifen release upon dissolution of the compositions was measured using HPLC-UV.

[0040] Figure 3 shows percentage dissolution and release of (Z)-endoxifen from exemplary sustained release compositions in the form of enteric coated delayed release tablets of low hardness (80N) and high hardness (120N) containing 4 mg of (Z)-endoxifen free base, and control (a 4 mg delayed release (Z)-endoxifen API-in-capsule), as measured according to USP I