HIGH DOSE ENDOXIFEN FORMULATIONS AND METHODS OF USE

CROSS-REFERENCE

[0001] The present application claims the benefit of U.S. Provisional Application No. 63/334,845, entitled "HIGH DOSE ENDOXIFEN FORMULATIONS AND METHODS OF USE," filed on April 26, 2022, and U.S. Provisional Application No. 63/437,048, entitled "HIGH DOSE ENDOXIFEN FORMULATIONS AND METHODS OF USE," filed on January 4, 2023, which applications are herein incorporated by reference in their entireties for all purposes.

BACKGROUND

[0002] While cancer survival rates have been increasing over the last few decades, cancer remains the second leading cause of death in the United States. Despite extensive research into treatments and prevention, drug resistance and relapse remain limiting factors in developing cancer cures. To combat these and other factors, there is a need for cancer therapies capable of effectively killing cancer cells, overcoming drug resistance, and preventing relapse.

SUMMARY

[0002a] In one aspect, the present disclosure refers to a composition comprising:

a drug formulation comprising:

not less than 5% and not more than 40% (Z)-endoxifen by weight, and

about 1.0% to about 10% of a disintegrant by weight of the total fill weight of the composition, and

an enteric-resistant delayed release capsule encapsulating the drug formulation.

[0002b] In another aspect, there is provided the use of the composition as defined above in the manufacture of a medicament for treating a disorder in a subject, wherein the composition is to be orally administered to the subject, wherein the disorder is a cancer, a hormone-dependent breast disorder, or a hormone-dependent reproductive tract disorder.

[0003] In various examples, the present disclosure provides a composition comprising: a drug formulation comprising: not less than 4% (Z)-endoxifen by weight, and not less than 1% croscarmellose sodium by weight; and an enteric-resistant delayed release capsule encapsulating the drug formulation.

[0004] In some examples, a percent of (Z)-endoxifen with respect to total endoxifen in the drug formulation is not less than 95%, not less than 97%, or not less than 98%, wherein the total endoxifen consists of (Z)-endoxifen and (E)-endoxifen. In some examples, the percent of (Z)-endoxifen with respect to total endoxifen in the drug formulation is not more than

100%. In some examples, the drug formulation comprises not less than 5%, not less than 7%, not less than 10%, not less than 12%, or not less than 15% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not more than 20%, not more than 22%, not more than 25%, not more than 30%, or not more than 40% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not less than 5% and not more than 40% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not less than 10% and not more than 25% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not less than 15% and not more than 20% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not less than 17% and not more than 19% (Z)-endoxifen by weight.

[0005] In some examples, the drug formulation comprises not less than 1 mg and not more than 80 mg (Z)-endoxifen per enteric-resistant delayed release capsule. In some examples, the drug formulation comprises not less than 10 mg and not more than 80 mg (Z)-endoxifen per enteric-resistant delayed release capsule. In some examples, the drug formulation comprises not less than 30 mg and not more than 50 mg (Z)-endoxifen per enteric-resistant delayed release capsule. In some examples, the drug formulation comprises not less than 38 mg and not more than 42 mg (Z)-endoxifen per enteric-resistant delayed release capsule. In some examples, the drug formulation comprises about 1 mg, about 2 mg, about 4 mg, about 10 mg, about 20 mg, about 40 mg, or about 80 mg (Z)-endoxifen per enteric-resistant delayed release capsule.

[0006] In some examples, the drug formulation comprises not less than 1.5%, not less than 1.7%, not less than 2%, not less than 2.2%, not less than 2.5%, not less than 2.7%, or not less than 2.8% croscarmellose sodium by weight. In some examples, the drug formulation comprises not more than 3%, not more than 3.2%, not more than 3.5%, not more than 4%, not more than 4.5%, or not more than 5% croscarmellose sodium by weight. In some examples, the drug formulation comprises not less than 1% and not more than 5% croscarmellose sodium by weight. In some aspects, the drug formulation comprises not less than 2% and not more than 4% croscarmellose sodium by weight. In some examples, the drug formulation comprises not less than 2.5% and not more than 3% croscarmellose sodium by weight. In some examples, the drug formulation comprises not less than 2.8% and not more than 3% croscarmellose sodium by weight.

[0007] In some examples, the drug formulation further comprises microcrystalline cellulose. In some examples, the drug formulation comprises not less than 60%, not less than 65%, not less than 70%, not less than 75%, or not less than 77% microcrystalline cellulose by weight. In some examples, the drug formulation comprises not more than 79%, not more than 80%, not more than 85%, not more than 90%, or not more than 95% microcrystalline cellulose by weight. In some examples, the drug formulation comprises not less than 60% and not more than 95% microcrystalline cellulose by weight. In some examples, the drug formulation comprises not less than 70% and not more than 90% microcrystalline cellulose by weight. In some examples, the drug formulation comprises not less than 75% and not more than 80% microcrystalline cellulose by weight.

[0008] In some examples, the drug formulation further comprises magnesium stearate. In some examples, the drug formulation comprises not less than 0.3%, not less than 0.5%, not less than 0.7%, not less than 0.8%, or not less than 0.9% magnesium stearate by weight. In some examples, the drug formulation comprises not more than 1.1%, not more than

1.2%, not more than 1.5%, not more than 1.8%, not more than 2%, or not more than 3% magnesium stearate by weight. In some examples, the drug formulation comprises not less than 0.5% and not more than 3%

magnesium stearate by weight. In some examples, the drug formulation comprises not less than 0.5% and not more than 2% magnesium stearate by weight. In some examples, the drug formulation comprises not less than 0.5% and not more than 1.5% magnesium stearate by weight.

[0009] In some examples, the enteric-resistant delayed release capsule comprises hydroxypropyl methylcellulose, gellan gum, gelatin, hydroxypropyl methylcellulose phthalate, a coloring agent, an opacifier, or any combination thereof. In some examples, the enteric-resistant delayed release capsule comprises hydroxypropyl methylcellulose. In some examples, the enteric-resistant delayed release capsule comprises not less than 85% and not more than 97% hydroxypropyl methylcellulose by weight. In some examples, the enteric-resistant delayed release capsule comprises gellan gum, gelatin, or a combination thereof. In some examples, the enteric-resistant delayed release capsule comprises not less than 3% and not more than 10% gellan gum, gelatin, or the combination thereof by weight.

[0010] In some examples, the (Z)-endoxifen comprises a polymorphic form of endoxifen.

[0011] In some examples, the polymorphic form of endoxifen is Form I, 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. In some examples, the x-ray powder diffraction pattern further comprises: a) at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta; b) at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta; or c) a combination thereof. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, or at least two peaks, at least three peaks selected from the group consisting of 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, or at least two peaks, at least three peaks selected from the group consisting of 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

[0012] In some examples, the polymorphic form of endoxifen is Form II, characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, and 14.0 ± 0.3°. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, or at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of the group consisting of 18.4 ± 0.3°, 22.0 ± 0.3°, 6.6 ± 0.3°, and 13.3 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, or at least two peaks, at least three peaks, at least four peaks, or at least five peaks selected from the group consisting of 20.0 ± 0.3°, 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

[0013] In some examples, the polymorphic form of endoxifen is Form III, characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, and 17.1 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least

one peak, or at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 17.7 ± 0.3°, 25.3 ± 0.3°, 18.2 ± 0.3°, and 22.5 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, or at least two peaks, at least three peaks, at least four peaks, or at least five peaks selected from the group consisting of 26.8 ± 0.3°, 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

[0014] In some examples, the polymorphic form of endoxifen is Form IV, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.7 ± 0.3° two theta, 23.3 ± 0.3°, and 13.6 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 23.8 ± 0.3°, 14.2 ± 0.3°, 22.5 ± 0.3°, or 15.7 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 7.1 ± 0.3°, 20.2 ± 0.3°, or 9.5 ± 0.3° two theta.

[0015] In some examples, the polymorphic form of endoxifen is Form V, characterized by an x-ray powder diffraction pattern comprising major peaks at 12.5 ± 0.3°, 19.6 ± 0.3°, and 8.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 21.7 ± 0.3°, 20.8 ± 0.3°, 19.8 ± 0.3°, or 16.0 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, comprises at least two peaks, at least three peaks, at least four peaks, at least five peaks, or at least six peaks selected from the group consisting of 21.7 ± 0.3°, 20.8 ± 0.3°, 19.8 ± 0.3°, 16.0 ± 0.3°, 22.0 ± 0.3°, 13.5 ± 0.3°, and 14.4 ± 0.3° two theta.

[0016] In some examples, the polymorphic form of endoxifen is Form VI, characterized by an x-ray powder diffraction pattern comprising major peaks at 9.9 ± 0.3°, 13.4 ± 0.3°, and 13.7 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 17.6 ± 0.3°, 18.6 ± 0.3°, 17.3 ± 0.3°, or 21.8 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 10.2 ± 0.3°, 19.5 ± 0.3°, or 14.2 ± 0.3° two theta.

[0017] In some examples, the polymorphic form of endoxifen is Form VII, characterized by an x-ray powder diffraction pattern comprising major peaks at 20.0 ± 0.3°, 22.6 ± 0.3°, and 10.6 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks

selected from the group consisting of 11.4 ± 0.3°, 16.4 ± 0.3°, 9.6 ± 0.3°, or 13.3 ± 0.3° two theta. In some examples, the

x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 18.2 ± 0.3°, 13.1 ± 0.3°, or 27.0 ± 0.3° two theta.

[0018] In some examples, the polymorphic form of endoxifen is Form VIII, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.8 ± 0.3°, 18.9 ± 0.3°, and 9.5 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 23.7 ± 0.3°, 21.9 ± 0.3°, 21.2 ± 0.3°, or 12.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 25.0 ± 0.3°, 21.5 ± 0.3°, or 16.4 ± 0.3° two theta.

[0019] In some examples, the polymorphic form of endoxifen is Form IX, characterized by an x-ray powder diffraction pattern comprising major peaks at 19.0 ± 0.3°, 12.9 ± 0.3°, and 15.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 21.7 ± 0.3°, 20.8 ± 0.3°, 21.1 ± 0.3°, or 8.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 16.4 ± 0.3°, 4.2 ± 0.3°, or 12.7 ± 0.3° two theta.

[0020] In some examples, the polymorphic form of endoxifen is Form X, characterized by an x-ray powder diffraction pattern comprising major peaks at 7.2 ± 0.3°, 14.3 ± 0.3°, 18.7 ± 0.3°, and two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 21.5 ± 0.3°, and 22.7 ± 0.3°, and 17.1 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 21.8 ± 0.3°, 27.3 ± 0.3°, or 29.4 ± 0.3° two theta.

[0021] In some examples, the polymorphic form of endoxifen is Form XI, characterized by an x-ray powder diffraction pattern comprising major peaks at 14.0 ± 0.3°, 17.7 ± 0.3°, and 11.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 18.4 ± 0.3°, 23.9 ± 0.3°, or 17.3 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 21.8 ± 0.3°, 20.8 ± 0.3°, and 23.0 ± 0.3°, or 22.2 ± 0.3° two theta.

[0022] In some examples, the polymorphic form of endoxifen is Form XII, characterized by an x-ray powder diffraction pattern comprising major peaks at 12.5 ± 0.3°, 15.6 ± 0.3°, and 19.0 ±

0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 21.9 ± 0.3°, 20.2 ± 0.3°, 16.0 ± 0.3°, or 21.6 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 22.4 ± 0.3°, 16.8 ± 0.3°, or 12.8 ± 0.3° two theta.

[0023] In some examples, the polymorphic form of endoxifen is Form XIV, characterized by an x-ray powder diffraction pattern comprising major peaks at 11.6 ± 0.3°, 21.3 ± 0.3°, and 19.3 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 17.5 ± 0.3°, 15.4 ± 0.3°, 21.6 ± 0.3°, or 5.8 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 16.3 ± 0.3°, 21.9 ± 0.3°, or 23.9 ± 0.3° two theta.

[0024] In some examples, the polymorphic form of endoxifen is Form XV, characterized by an x-ray powder diffraction pattern comprising major peaks at 9.8 ± 0.3°, 4.7 ± 0.3°, and 14.0 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 20.2 ± 0.3°, 7.1 ± 0.3°, 23.4 ± 0.3°, or 22.4 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 21.7 ± 0.3°, 22.7 ± 0.3°, or 18.8 ± 0.3° two theta.

[0025] In some examples, the polymorphic form of endoxifen is Form XIX, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.7 ± 0.3°, 23.6 ± 0.3°, and 18.9 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, at least three peaks, or at least four peaks selected from the group consisting of 9.4 ± 0.3°, 23.3 ± 0.3°, 22.3 ± 0.3°, or 20.1 ± 0.3° two theta. In some examples, the x-ray powder diffraction pattern further comprises at least one peak, at least two peaks, or at least three peaks selected from the group consisting of 19.6 ± 0.3°, 7.1 ± 0.3°, or 15.7 ± 0.3° two theta.

[0026] In some examples, at least 90% of the (Z)-endoxifen by weight is the polymorphic form of endoxifen.

[0027] In some examples, the composition comprises an in vitro dissolution profile wherein: a) not more than 20% of the (Z)-endoxifen is released within 2 hours after the

composition is introduced into an acidic stage of an in vitro dissolution assay; b) not less than 70% of the (Z)-

endoxifen is released within 1.5 hours after the composition is introduced into a buffer stage of the in vitro dissolution assay; or c) a combination thereof. In some examples, not more than 5%, not more than 10%, or not more than 15% of the (Z)-endoxifen is released within 2 hours after the composition is introduced into the acidic stage of the in vitro dissolution assay. In some examples, not less than 75%, not less than 80%, or not less than 85% of the (Z)-endoxifen is released within 1.5 hours after the composition is introduced into the buffer stage of the in vitro dissolution assay. In some examples, the buffer stage comprises a pH of less than 2. In some examples, the buffer stage comprises a pH of about 6.8. In some examples, the buffer stage comprises 0.75% polysorbate 80. In some examples, upon oral administration of the composition to a subject not more than 5%, not more than 10%, not more than 15%, or not more than 20% of the (Z)-endoxifen is released in a stomach of the subject, and not less than 70%, not less than 75%, not less than 80%, or not less than 85% of the (Z)-endoxifen is released in an intestine of the subject.

[0028] In various examples, the present disclosure provides a composition comprising: a drug formulation comprising: not less than 15% and not more than 20% (Z)-endoxifen by weight, not less than 2% and not more than 4% croscarmellose sodium by weight, not less than 0.5% and not more than 2% magnesium stearate by weight, and not less than 70% and not more than 80% microcrystalline cellulose by weight; and an enteric-resistant delayed release capsule encapsulating the drug formulation, wherein the enteric-resistant delayed release capsule comprises: not less than 85% and not more than 97% hydroxypropyl methylcellulose by weight, and not less than 3% and not more than 7% gellan gum by weight.

[0029] In some examples, the drug formulation comprises not less than 17% and not more than 19% (Z)-endoxifen by weight. In some examples, the drug formulation comprises not less than 2.8% and not more than 3% croscarmellose sodium by weight. In some examples, the drug formulation comprises not less than 0.7% and not more than 1.2% magnesium stearate by weight. In some examples, the drug formulation comprises not less than 75% and not more than 80% microcrystalline cellulose by weight.

[0030] In various examples, the present disclosure provides a method of treating a disorder in a subject, the method comprising orally administering to the subject a composition comprising: a drug formulation comprising: not less than 4% (Z)-endoxifen by weight, and not less than 1% croscarmellose sodium by weight; and an enteric-resistant delayed release capsule encapsulating the drug formulation thereby treating the cancer.

[0031] In various examples, the present disclosure provides a method of treating a disorder in a subject, the method comprising orally administering to the subject a composition as described herein, thereby treating the disorder.

[0032] In some examples, the disorder is a cancer, a hormone-dependent breast disorder, or a hormone-dependent reproductive tract disorder. In some examples, the cancer is breast cancer, cervical cancer, ovarian cancer, endometrial cancer, uterine cancer, vaginal cancer, vulvar cancer, melanoma, colorectal cancer, gastric cancer, neuroblastoma, pancreatic cancer, esophageal cancer, rectal cancer, or cholangiocarcinoma. In some examples, the breast cancer is triple negative breast cancer, ductal carcinoma in situ, lobular carcinoma in situ, invasive ductal carcinoma, or invasive lobular carcinoma. In some examples, the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, precocious puberty, or McCune-Albright Syndrome. In some examples, the disorder is tamoxifen-resistant or tamoxifen-refractory.

[0033] In some examples, the method further comprises releasing not more than 5%, not more than 10%, not more than 15%, or not more than 20% of the (Z)-endoxifen is released in a stomach of the subject, and not less than 70%, not less than 75%, not less than 80%, or not less than 85% of the (Z)-endoxifen is released in an intestine of the subject following oral administration of the composition. In some examples, the method further comprises producing in the subject a blood plasma concentration of endoxifen that is not less than 70%, not less than 75%, not less than 80%, or not less than 85% in the (Z)-isoform.

INCORPORATION BY REFERENCE

[0034] 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

[0035] 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:

[0036] **FIG. 1A** shows an HPLC chromatogram of a 40 mg (Z)-endoxifen formulation containing 40 mg (Z)-endoxifen, 173.78 mg microcrystalline cellulose, 6.50 mg croscarmellose sodium, and 2.23 mg magnesium stearate encapsulated in an enteric-resistant delayed release capsule and dissolved in a diluent to a concentration of to 0.5 mg/mL (Z)-endoxifen.

[0037] **FIG. 1B** shows an HPLC chromatogram of a 0.5 mg/mL (Z)-endoxifen reference sample encapsulated in an enteric-resistant delayed release capsule and dissolved in diluent.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising:

a drug formulation comprising:

not less than 5% and not more than 40% (Z)-endoxifen by weight, and

about 1.0% to about 10% of a disintegrant by weight of the total fill weight of the composition, and

an enteric-resistant delayed release capsule encapsulating the drug formulation.

2. The composition of claim 1, wherein the disintegrant is selected from the group consisting of croscarmellose sodium, agar, alginic acid, calcium carbonate, microcrystalline cellulose, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, clays, gums, and combinations thereof.

3. The composition of claim 1, wherein the disintegrant is crospovidone.

4. The composition of claim 1, wherein the disintegrant is sodium starch glycolate.

5. The composition of claim 1, wherein the disintegrant is croscarmellose sodium.

6. The composition of claim 1, wherein the drug formulation comprises:

not less than 1% and not more than 5% of the disintegrant by weight of the total fill weight of the composition; or

not less than 2% and not more than 4% of the disintegrant by weight of the total fill weight of the composition.

7. The composition of claim 1, wherein the drug formulation comprises:

not less than 10% and not more than 25% (Z)-endoxifen by weight;

not less than 15% and not more than 20% (Z)-endoxifen by weight; or

not less than 17% and not more than 19% (Z)-endoxifen by weight.

8. The composition of claim 1, wherein the drug formulation comprises from about 10 mg to about 100 mg, from about 10 mg to about 80 mg, from about 10 mg to about 50 mg, from about

20 mg to about 50 mg, from about 30 mg to about 50 mg, or from about 10 mg to about 30 mg of (Z)-endoxifen per enteric-resistant delayed release capsule.

9. The composition of claim 1, wherein the drug formulation comprises about 10 mg, about 20 mg, about 40 mg, or about 80 mg of (Z)-endoxifen per enteric-resistant delayed release capsule.

10. The composition of claim 1, wherein the drug formulation further comprises microcrystalline cellulose.

11. The composition of claim 10, wherein the drug formulation comprises:

from about 50% to about 95% microcrystalline cellulose by weight of the total fill weight of the composition;

not less than 60% and not more than 95% microcrystalline cellulose by weight of the total fill weight of the composition;

not less than 70% and not more than 90% microcrystalline cellulose by weight of the total fill weight of the composition; or

not less than 75% and not more than 80% microcrystalline cellulose by weight of the total fill weight of the composition.

12. The composition of claim 1, wherein the drug formulation further comprises magnesium stearate.

13. The composition of claim 12, wherein the drug formulation comprises:

not less than 0.5% and not more than 3% magnesium stearate by weight of the total fill weight of the composition;

not less than 0.5% and not more than 2% magnesium stearate by weight of the total fill weight of the composition; or

not less than 0.5% and not more than 1.5% magnesium stearate by weight of the total fill weight of the composition.

14. The composition of claim 1, wherein the enteric-resistant delayed release capsule comprises hydroxypropyl methylcellulose, gellan gum, gelatin, hydroxypropyl methylcellulose phthalate, a coloring agent, an opacifier, or any combination thereof.

15. The composition of claim 1 or claim 14, wherein the enteric-resistant delayed release capsule comprises hydroxypropyl methylcellulose.

16. The composition of claim 15, wherein the enteric-resistant delayed release capsule comprises not less than 85% and not more than 97% hydroxypropyl methylcellulose by weight relative to total capsule weight.

17. The composition of claim 1 or claim 14, wherein the enteric-resistant delayed release capsule comprises gellan gum, gelatin, or a combination thereof.

18. The composition of claim 17, wherein the enteric-resistant delayed release capsule comprises not less than 3% and not more than 10% the gellan gum, the gelatin, or the combination thereof by weight relative to total capsule weight.

19. The composition of claim 1, wherein the enteric-resistant delayed release capsule comprises from about from about 65% to about 95% hydroxypropyl methylcellulose by weight relative to total capsule weight and from about 3% to about 10% gellan gum by weight relative to total capsule weight.

20. The composition of claim 1, wherein the (Z)-endoxifen comprises a polymorphic form of endoxifen, wherein the polymorphic form of the endoxifen is:

Form I, 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;

Form II, characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, and 14.0 ± 0.3° two theta;

Form III, characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, and 17.1 ± 0.3° two theta;

Form IV, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.7 ± 0.3° two theta, 23.3 ± 0.3°, and 13.6 ± 0.3° two theta;

Form V, characterized by an x-ray powder diffraction pattern comprising major peaks at 12.5 ± 0.3°, 19.6 ± 0.3°, and 8.9 ± 0.3° two theta;

Form VI, characterized by an x-ray powder diffraction pattern comprising major peaks at 9.9 ± 0.3°, 13.4 ± 0.3°, and 13.7 ± 0.3° two theta;

Form VII, characterized by an x-ray powder diffraction pattern comprising major peaks at 20.0 ± 0.3°, 22.6 ± 0.3°, and 10.6 ± 0.3° two theta;

Form VIII, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.8 ± 0.3°, 18.9 ± 0.3°, and 9.5 ± 0.3° two theta;

Form IX, characterized by an x-ray powder diffraction pattern comprising major peaks at 19.0 ± 0.3°, 12.9 ± 0.3°, and 15.9 ± 0.3° two theta;

Form X, characterized by an x-ray powder diffraction pattern comprising major peaks at 7.2 ± 0.3°, 14.3 ± 0.3°, 18.7 ± 0.3°, and two theta;

Form XI, characterized by an x-ray powder diffraction pattern comprising major peaks at 14.0 ± 0.3°, 17.7 ± 0.3°, and 11.9 ± 0.3° two theta;

Form XII, characterized by an x-ray powder diffraction pattern comprising major peaks at 12.5 ± 0.3°, 15.6 ± 0.3°, and 19.0 ± 0.3° two theta;

Form XIV, characterized by an x-ray powder diffraction pattern comprising major peaks at 11.6 ± 0.3°, 21.3 ± 0.3°, and 19.3 ± 0.3° two theta;

Form XV, characterized by an x-ray powder diffraction pattern comprising major peaks at 9.8 ± 0.3°, 4.7 ± 0.3°, and 14.0 ± 0.3° two theta;

Form XIX, characterized by an x-ray powder diffraction pattern comprising major peaks at 4.7 ± 0.3°, 23.6 ± 0.3°, and 18.9 ± 0.3° two theta; or

a combination thereof.

21. The composition of claim 20, wherein at least 90% of the (Z)-endoxifen by weight is the polymorphic form of endoxifen.

22. The composition of claim 1, comprising an *in vitro* dissolution profile wherein:

a) not more than 20% of the (Z)-endoxifen is released within 2 hours after the composition is introduced into an acidic stage of an *in vitro* dissolution assay;

b) not less than 70% of the (Z)-endoxifen is released within 1.5 hours after the composition is introduced into a buffer stage of the *in vitro* dissolution assay; or

c) a combination thereof.

23. The composition of claim 1, wherein

a) not more than 20% of the (Z)-endoxifen is released within 2 hours after the composition is introduced into an acidic stage of an in vitro dissolution assay;

b) not less than 70% of the (Z)-endoxifen is released within 1.5 hours after the composition is introduced into a buffer stage of the in vitro dissolution assay; or

c) a combination thereof,

wherein:

the acidic stage comprises a pH of less than 2 and the buffer stage comprises a pH of about 6.8.

24. The composition of claim 1, comprising:

a drug formulation comprising:

not less than 15% and not more than 20% (Z)-endoxifen by weight,

not less than 2% and not more than 4% croscarmellose sodium by weight,

not less than 0.5% and not more than 2% magnesium stearate by weight, and

not less than 70% and not more than 80% microcrystalline cellulose by weight; and

an enteric-resistant delayed release capsule encapsulating the drug formulation, wherein the enteric-resistant delayed release capsule comprises:

not less than 85% and not more than 97% hydroxypropyl methylcellulose by weight, and

not less than 3% and not more than 7% gellan gum by weight.

25. Use of the composition of claim 1 in the manufacture of a medicament for treating a disorder in a subject, wherein the composition is to be orally administered to the subject, wherein the disorder is a cancer, a hormone-dependent breast disorder, or a hormone-dependent reproductive tract disorder.

26. The use of claim 25, wherein the cancer is breast cancer, cervical cancer, ovarian cancer, endometrial cancer, uterine cancer, vaginal cancer, vulvar cancer, melanoma, colorectal cancer, gastric cancer, neuroblastoma, pancreatic cancer, esophageal cancer, rectal cancer, or cholangiocarcinoma.

27. The use of claim 26, wherein the breast cancer is triple negative breast cancer, ductal carcinoma *in situ*, lobular carcinoma *in situ*, invasive ductal carcinoma, or invasive lobular carcinoma.

28. The use of claim 25, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, precocious puberty, or McCune-Albright Syndrome.

29. The use of claim 25, wherein the disorder is a tamoxifen-resistant disorder or a tamoxifen-refractory disorder.

30. The use of claim 29, wherein the tamoxifen-resistant disorder or the tamoxifen-refractory disorder is a tamoxifen-resistant or a tamoxifen-refractory cancer.